

- ▣ **CARNITOR®** (levocarnitine) Tablets USP 330 mg
- ▣ **CARNITOR®** (levocarnitine) Oral Solution USP 1 g/10 mL
- ▣ **CARNITOR®** (levocarnitine) Injection USP
1 g/5 mL (200 mg/mL)

THERAPEUTIC CLASSIFICATION

Replenisher (Carnitine)

ACTIONS AND 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.

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. 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 such 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. In one study, BUN, creatinine, and phosphorus blood levels decreased with CARNITOR® administration. In another study, increases in hematocrit, decreases in hypotensive episodes, and improvement in well being have been observed, although not statistically significant.

INDICATIONS AND CLINICAL USAGE

**CARNITOR® (levocarnitine) Oral Solution (1g/10mL Multidose),
330 mg Tablet and Injection (1 g per 5 mL)**

CARNITOR® is indicated in the treatment of primary systemic carnitine deficiency. In the reported cases, the clinical presentation consisted of recurrent episodes of Reye-like encephalopathy, hypoketotic hypoglycemia, and/or cardiomyopathy. Associated symptoms included hypotonia, muscle weakness and failure to thrive. A diagnosis of primary carnitine deficiency requires that serum, red cell and/or tissue carnitine levels be low and that the patient does not have a primary defect in fatty acid or organic acid oxidation (see **ACTIONS AND CLINICAL PHARMACOLOGY**). 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.

CARNITOR® is also indicated for acute and chronic treatment of patients with an inborn error of metabolism which results in a secondary carnitine deficiency.

CARNITOR® Injection (1 g per 5 mL)

CARNITOR® Injection is also indicated 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

General

The safety and efficacy of oral levocarnitine has not been evaluated in patients with renal insufficiency. Chronic administration of high doses of oral levocarnitine in patients with severely compromised renal function or in ESRD patients on dialysis may result in accumulation of the potentially toxic metabolites, trimethylamine (TMA) and trimethylamine-N-oxide (TMAO), since these metabolites are normally excreted in the urine.

CARNITOR® (levocarnitine) Oral Solution

CARNITOR® Oral Solution is for oral/internal use only.

Gastrointestinal reactions may result from a too rapid consumption of carnitine. CARNITOR® Oral Solution may be consumed alone, or dissolved 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.

CARNITOR® Injection

CARNITOR® Injection is for intravenous use only.

CARNITOR® Oral Solution, 330 mg Tablet and Injection

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.

ADVERSE REACTIONS

CARNITOR® (levocarnitine) Oral Solution and 330 mg Tablet

Various mild gastrointestinal complaints have been reported during the long-term administration of oral L- or D,L-carnitine; these include transient nausea and vomiting, abdominal cramps, and diarrhea. Mild myasthenia has been described only in uremic patients receiving D,L-carnitine. Gastrointestinal adverse reactions with CARNITOR® Oral Solution dissolved in liquids might be avoided by a slow consumption of the solution or by a greater dilution. Decreasing the dosage often diminishes 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.

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.

CARNITOR® Injection

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 \geq 5% Regardless of Causality by Body System					
	Placebo (n=63)	Levo- carnitine 10 mg (n=34)	Levo- carnitine 20 mg (n=62)	Levo- carnitine 40 mg (n=34)	Levo- carnitine 10, 20 & 40 mg (n=130)
<i>Body as Whole</i>					
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
<i>Cardiovascular</i>					
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
<i>Digestive</i>					
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
<i>Endocrine System</i>					
Parathyroid disorder	2	6	2	6	4
<i>Hemic/Lymphatic</i>					
Anemia	3	3	5	12	6
<i>Metabolic/Nutritional</i>					
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
<i>Musculo-Skeletal</i>					
Leg cramps	13		8		4
Myalgia	6				
<i>Nervous</i>					
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
<i>(continued)</i>					

Adverse Events with a Frequency \geq 5% Regardless of Causality by Body System (continued)					
	Placebo (n=63)	Levo- carnitine 10 mg (n=34)	Levo- carnitine 20 mg (n=62)	Levo- carnitine 40 mg (n=34)	Levo- carnitine 10, 20 & 40 mg (n=130)
<i>Respiratory</i>					
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
<i>Skin And Appendages</i>					
Pruritus	13		8	3	5
Rash	3		5	3	3
<i>Special Senses</i>					
Amblyopia	2		6		3
Eye disorder	3	6	3		3
Taste perversion			2	9	3
<i>Urogenital</i>					
Urinary tract infect	6	3	3		2
Kidney failure	5	6	6	6	6

SYMPTOMS AND TREATMENT OF OVERDOSAGE

There have been no reports of toxicity from levocarnitine overdosage. Levocarnitine is easily removed from plasma by dialysis. The intravenous LD₅₀ of levocarnitine in rats is 5.4 g/kg and the oral LD₅₀ of levocarnitine in mice is 19.2 g/kg. Carnitine may cause diarrhea. Overdosage should be treated with supportive care.

DOSSAGE AND ADMINISTRATION

CARNITOR® (levocarnitine) Oral Solution

For oral use only. **Not for parenteral use.**

Adults

The recommended dosage of levocarnitine is 1 to 3 g/day for a 50 kg subject, which is equivalent to 10 to 30 mL/day of CARNITOR® 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 levocarnitine is 50 to 100 mg/kg/day which is equivalent to 0.5 mL/kg/day CARNITOR® 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 50 mg/kg/day, and be increased slowly to a maximum of 3 g/day (30 mL/day) while assessing tolerance and therapeutic response. Monitoring should include periodic blood chemistries, vital signs, plasma carnitine concentrations, and overall clinical condition.

CARNITOR® Oral Solution may be consumed alone or dissolved in drink or other liquid food. Doses should be spaced evenly throughout the day (every three or four hours) preferably during or following meals and should be consumed slowly in order to maximize tolerance.

CARNITOR® 330 mg Tablet

CARNITOR® Tablets are for oral administration only.

Adults

The recommended oral dosage for adults is 990 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/kg/day in divided doses, with a maximum of 3 g/day. Dosage should begin at 50 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® Injection

Metabolic Disorders

CARNITOR® Injection is administered intravenously. 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 micromoles/liter at baseline) and overall clinical condition.

ESRD Patients on Hemodialysis

The recommended dose is 20 mg/kg dry body weight as a slow 2 - 3 minute bolus injection into the venous return line after each dialysis session. It is recommended that therapy begin after being on hemodialysis for a period of six months. Post-dialysis levocarnitine plasma levels approach physiological levels after approximately two months of therapy at 20 mg/kg. After two months of therapy and based on clinical assessment, the dose may be adjusted to 5 mg/kg after each dialysis session.

Compatibility/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 4000 mg/500 mL (8.0 mg/mL) and stored at room temperature (25°C) for up to 24 hours in PVC plastic bags.

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

Pediatric Dosage

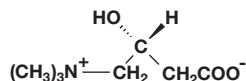
See **DOSAGE AND ADMINISTRATION**.

PHARMACEUTICAL INFORMATION

Proper or Common Name (USAN) Levocarnitine

Chemical Name 3-carboxy-2(R)-hydroxy-N,N,N-trimethyl-1-propanaminium, inner salt.

Structural Formula



Molecular Weight 161.20

Molecular Formula C₇H₁₅NO₃

Description

Levocarnitine is a carrier molecule in the transport of long-chain fatty acids across the inner mitochondrial membrane. As a bulk drug substance it is a white, crystalline, hygroscopic powder with a melting point of 196-197°C. It is readily soluble in water, hot alcohol, and insoluble in acetone. The pH of a solution (1 in 20) is between 6-8 and its pKa value is 3.8.

Composition

Each 118 mL container of **CARNITOR® (levocarnitine) Oral Solution** contains 1 g of levocarnitine/10 mL. Also contains: Artificial Cherry Flavor, D,L-Malic Acid, Purified Water, Sucrose Syrup. Methylparaben NF and Propylparaben NF are added as preservatives. The pH is approximately 5.

Each **CARNITOR® Tablet** contains 330 mg of levocarnitine and the inactive ingredients magnesium stearate, microcrystalline cellulose and povidone.

CARNITOR® Injection is a sterile aqueous solution with a levocarnitine concentration of 200 milligrams per milliliter. Each 5 mL vial contains 1 g of levocarnitine. The pH is adjusted to 6.0 to 6.5 with hydrochloric acid and/or sodium hydroxide.

Recommended Storage Conditions

CARNITOR® Oral Solution should be stored at room temperature (15 - 30°C). Avoid excessive heat. Protect from freezing. Store upright.

CARNITOR® Tablets should be stored at room temperature (15 - 30°C). Avoid excessive heat. Protect from freezing. Do not store after removal from foil packaging; contents hygroscopic.

CARNITOR® Injection should be stored at room temperature (15 - 30°C). Avoid excessive heat. Protect from freezing. Supplied in single dose vials; discard unused portion after opening. Contains no preservatives; levocarnitine will support microbial growth.

AVAILABILITY OF DOSAGE FORMS

CARNITOR® (levocarnitine) Oral Solution 1 g/10 mL is a clear, cherry flavored oral solution supplied in 118 mL (4 FL. OZ.) multiple-unit plastic containers. The multiple-unit containers are packaged 24 per case. **For oral use only.**

CARNITOR® Tablets are supplied as 330 mg white, biconvex tablets embossed with CARNITOR® ST and packaged in single unit blisters of laminated aluminum foil. There are 10 tablets per blister card and nine cards per carton for a total of 90 tablets per carton. **For oral use only.**

CARNITOR® Injection is a sterile aqueous solution containing 200 milligrams of levocarnitine per mL. It is available in 5 mL single-dose vials, packaged 5 vials per carton. **For intravenous use only.**

INFORMATION FOR THE CONSUMER

No additional information for the consumer is available.

MICROBIOLOGY (if applicable)

Not applicable.

PHARMACOLOGY

Metabolism and Excretion

In a pharmacokinetic study where five normal adult male volunteers received an oral dose of [³H-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 [³H-methyl]-L-carnitine in serum occurred from 2.0 to 4.5 hr after drug administration. After oral administration, the unabsorbed levocarnitine is metabolized in the gastrointestinal tract by the bacterial microflora to trimethylamine and γ-butyrobetaine. Trimethylamine is absorbed and converted to trimethylamine N-oxide which is primarily excreted in urine. [³H]-γ-butyrobetaine is excreted primarily in feces (0.44% to 45% of the administered dose). Urinary excretion of levocarnitine was 4% to 8% of the dose. Fecal excretion of total carnitine was less than 2% of the administered dose.

After attainment of steady state following 4 days of oral administration of CARNITOR® (levocarnitine) Tablets (1980 mg q12h) or Oral Solution (2000 mg q12h) 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).

Bioavailability/Pharmacokinetics

In a relative bioavailability study in 15 healthy adult male volunteers, CARNITOR® Tablets were found to be bioequivalent to CARNITOR® Oral Solution. Following the administration of 6 tablets of CARNITOR® 330 mg b.i.d. or 2g of CARNITOR® oral solution b.i.d., the maximum plasma concentration (C_{max}) was 80 nmol/mL and the time to maximum plasma concentration (T_{max}) occurred at 3.3 hours. Based on confidence - interval testing procedure (two one-sided t test with 90% confidence intervals within 80 - 120% range), the two oral formulations were found to be bio-equivalent.

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 73.1 ± 16% 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/hr. Endogenous baseline levels were not subtracted since total body clearance of levocarnitine does not distinguish between exogenous sources of levocarnitine and endogenously synthesized levocarnitine. The steady state volume of distribution (V_{ss}) of the intravenously administered dose above baseline endogenous levels was calculated to be a mean of 29.0 L ± 7.1 L (approximately 0.39 L/kg) which is an underestimate of the true V_{ss} since plasma levocarnitine is known to equilibrate slowly with, for instance, muscle levocarnitine.

Levocarnitine was not bound to plasma protein or albumin when tested at any concentration or with any species including the human.

The pharmacokinetics of levocarnitine in 12 ESRD patients undergoing hemodialysis for at least six months was studied following single and multiple post-dialysis i.v. administration of 20 mg/kg of CARNITOR®, three times a week for nine consecutive weeks. Prior to dosing with CARNITOR®, endogenous plasma levels of levocarnitine in these patients were approximately 20 nmol/mL pre-dialysis and 5.6 nmol/mL post-dialysis. Endogenous plasma levels of levocarnitine in normals are approximately 40 - 50 nmol/mL. Following repeated post-dialysis i.v. administration of 20 mg/kg of CARNITOR®, the pre-dose, post-dialysis plasma concentration of levocarnitine was restored to physiological levels (40 nmol/mL) in about eight weeks.

Plasma levels were determined in two controlled clinical trials in patients on dialysis for at least six months. Levels before CARNITOR® administration were below normal. Intravenous administration of CARNITOR® increased levels in a similar manner to the pharmacokinetics study. A linear relationship between levocarnitine plasma levels and i.v. doses of CARNITOR® (10, 20 and 40 mg/kg) was found.



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