

CENTER FOR DRUG EVALUATION AND RESEARCH

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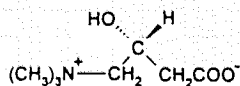
CARNITOR[®] (levocarnitine)

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: C₇H₁₅NO₃

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

37 deficiency and which are due to an underlying organic acidemia, as
38 symptoms of both abnormalities may be expected to improve with
39 CARNITOR®. The literature reports that carnitine can promote the
40 excretion of excess organic or fatty acids in patients with defects in
41 fatty acid metabolism and/or specific organic acidopathies that
42 bioaccumulate acylCoA esters.¹⁻⁶

43
44 Secondary carnitine deficiency can be a consequence of inborn
45 errors of metabolism or iatrogenic factors such as hemodialysis.
46 CARNITOR® may alleviate the metabolic abnormalities of patients
47 with inborn errors that result in accumulation of toxic organic acids.
48 Conditions for which this effect has been demonstrated are: glutaric
49 aciduria II, methyl malonic aciduria, propionic acidemia, and medium
50 chain fatty acylCoA dehydrogenase deficiency.^{7,8} Autointoxication
51 occurs in these patients due to the accumulations of acylCoA
52 compounds that disrupt intermediary metabolism. The subsequent
53 hydrolysis of the acylCoA compound to its free acid results in acidosis
54 which can be life-threatening. Levocarnitine clears the acylCoA
55 compound by formation of acylcarnitine, which is quickly excreted.
56 Carnitine deficiency is defined biochemically as abnormally low
57 plasma concentrations of free carnitine, less than 20 µmol/L at one
58 week post term and may be associated with low tissue and/or urine
59 concentrations. Further, this condition may be associated with a
60 plasma concentration ratio of acylcarnitine/levocarnitine greater than
61 0.4 or abnormally elevated concentrations of acylcarnitine in the
62 urine. In premature infants and newborns, secondary deficiency is
63 defined as plasma levocarnitine concentrations below age-related
64 normal concentrations.

65
66 End Stage Renal Disease (ESRD) patients on maintenance
67 hemodialysis may have low plasma carnitine concentrations and an
68 increased ratio of acylcarnitine/carnitine because of reduced intake of
69 meat and dairy products, reduced renal synthesis, and dialytic losses.
70 Certain clinical conditions common in hemodialysis patients as
71 malaise, muscle weakness, cardiomyopathy and cardiac arrhythmias
72 may be related to abnormal carnitine metabolism.

73

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

77

78 PHARMACOKINETICS

79 In a relative bioavailability study in 15 healthy adult male volunteers
80 CARNITOR® Tablets were found to be bio-equivalent to CARNITOR®
81 Oral Solution. Following 4 days of dosing with 6 tablets of
82 CARNITOR® 330 mg bid or 2 g of CARNITOR® oral solution bid, the
83 maximum plasma concentration (C_{max}) was about 80 $\mu\text{mol/L}$ and the
84 time to maximum plasma concentration (T_{max}) occurred at 3.3 hours.

85

86 The plasma concentration profiles of levocarnitine after a slow 3
87 minute intravenous bolus dose of 20 mg/kg of CARNITOR® were
88 described by a two-compartment model. Following a single i.v.
89 administration, approximately 76% of the levocarnitine dose was
90 excreted in the urine during the 0-24h interval. Using plasma
91 concentrations uncorrected for endogenous levocarnitine, the mean
92 distribution half life was 0.585 hours and the mean apparent terminal
93 elimination half life was 17.4 hours.

94

95 The absolute bioavailability of levocarnitine from the two oral
96 formulations of CARNITOR®, calculated after correction for circulating
97 endogenous plasma concentrations of levocarnitine, was $15.1 \pm 5.3\%$
98 for CARNITOR® Tablets and $15.9 \pm 4.9\%$ for CARNITOR® Oral
99 Solution.

100

101 Total body clearance of levocarnitine (Dose/AUC including
102 endogenous baseline concentrations) was a mean of 4.00 L/h.

103

104 Levocarnitine was not bound to plasma protein or albumin when
105 tested at any concentration or with any species including the human.⁹

106

107 In a 9-week study, 12 ESRD patients undergoing hemodialysis for at
108 least 6 months received CARNITOR® 20 mg/kg three times per week
109 after dialysis. Prior to initiation of CARNITOR® therapy, mean plasma
110 levocarnitine concentrations were approximately 20 $\mu\text{mol/L}$ pre-

111 dialysis and 6 $\mu\text{mol/L}$ post-dialysis. The table summarizes the
112 pharmacokinetic data (mean \pm SD $\mu\text{mol/L}$) after the first dose of
113 CARNITOR[®] and after 8 weeks of CARNITOR[®] therapy.

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

114
115 After one week of CARNITOR[®] therapy (3 doses), all patients had
116 trough concentrations between 54 and 180 $\mu\text{mol/L}$ (normal 40-50
117 $\mu\text{mol/L}$) and concentrations remained relatively stable or increased
118 over the course of the study.

119
120 In a similar study in ESRD patients also receiving 20 mg/kg
121 CARNITOR[®] 3 times per week after hemodialysis, 12 and 24-week
122 mean pre-dialysis (trough) levocarnitine concentrations were 189
123 (N=25) and 243 (N=23) $\mu\text{mol/L}$, respectively.

124
125 In a dose-ranging study in ESRD patients undergoing hemodialysis,
126 patients received 10, 20, or 40 mg/kg CARNITOR[®] 3 times per week
127 following dialysis (N~30 for each dose group). Mean \pm SD trough
128 levocarnitine concentrations ($\mu\text{mol/L}$) by dose after 12 and 24 weeks
129 of therapy are summarized in the table.

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

130
131 While the efficacy of CARNITOR[®] to increase carnitine concentrations
132 in patients with ESRD undergoing dialysis has been demonstrated,
133 the effects of supplemental carnitine on the signs and symptoms of
134 carnitine deficiency and on clinical outcomes in this population have
135 not been determined.

136

137 **METABOLISM AND EXCRETION**

138 In a pharmacokinetic study where five normal adult male volunteers
139 received an oral dose of [³H-methyl]-L-carnitine following 15 days of a

140 high carnitine diet and additional carnitine supplement, 58 to 65% of
141 the administered radioactive dose was recovered in the urine and
142 feces in 5 to 11 days. Maximum concentration of [³H-methyl]-L-
143 carnitine in serum occurred from 2.0 to 4.5 hr after drug
144 administration. Major metabolites found were trimethylamine N-oxide,
145 primarily in urine (8% to 49% of the administered dose) and [³H]-γ-
146 butyrobetaine, primarily in feces (0.44% to 45% of the administered
147 dose). Urinary excretion of levocarnitine was about 4 to 8% of the
148 dose. Fecal excretion of total carnitine was less than 1% of the
149 administered dose.¹⁰

150

151 After attainment of steady state following 4 days of oral administration
152 of CARNITOR® Tablets (1980 mg q 12h) or Oral Solution (2000 mg q
153 12h) to 15 healthy male volunteers, the mean urinary excretion of
154 levocarnitine during a single dosing interval (12h) was about 9% of
155 the orally administered dose (uncorrected for endogenous urinary
156 excretion).

157

158 **INDICATIONS AND USAGE**

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

161

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

164

165 **CONTRAINDICATIONS**

166 None known.

167

168 **WARNINGS**

169 None.

170

171 **PRECAUTIONS**

172 **Carcinogenesis, mutagenesis, impairment of fertility**

173 Mutagenicity tests performed in *Salmonella typhimurium*,
174 *Saccharomyces cerevisiae*, and *Schizosaccharomyces pombe*
175 indicate that levocarnitine is not mutagenic. No long-term animal

176 studies have been performed to evaluate the carcinogenic potential of
177 levocarnitine.

178

179 **PREGNANCY**

180 **Pregnancy Category B.**

181 Reproductive studies have been performed in rats and rabbits at
182 doses up to 3.8 times the human dose on the basis of surface area
183 and have revealed no evidence of impaired fertility or harm to the
184 fetus due to CARNITOR®. There are, however, no adequate and well
185 controlled studies in pregnant women.

186

187 Because animal reproduction studies are not always predictive of
188 human response, this drug should be used during pregnancy only if
189 clearly needed.

190

191 **NURSING MOTHERS**

192 Levocarnitine supplementation in nursing mothers has not been
193 specifically studied.

194

195 Studies in dairy cows indicate that the concentration of levocarnitine
196 in milk is increased following exogenous administration of
197 levocarnitine. In nursing mothers receiving levocarnitine, any risks to
198 the child of excess carnitine intake need to be weighed against the
199 benefits of levocarnitine supplementation to the mother.
200 Consideration may be given to discontinuation of nursing or of
201 levocarnitine treatment.

202

203 **PEDIATRIC USE**

204 See Dosage and administration.

205

206 **ADVERSE REACTIONS**

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

211

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 $\geq 5\%$ are reported without regard to causality.

**Adverse Events with a Frequency $\geq 5\%$ 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 LD₅₀ of levocarnitine in rats is 5.4 g/kg and the oral LD₅₀ of levocarnitine in mice is 19.2 g/kg. Large doses of levocarnitine may cause diarrhea.

232 **DOSAGE AND ADMINISTRATION**

233

234 CARNITOR® Injection is administered intravenously.

235

236 ***Metabolic Disorders***

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

245

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

252

253 ***ESRD Patients on Hemodialysis***

254 The recommended starting dose is 10-20 mg/kg dry body weight as a
255 slow 2-3 minute bolus injection into the venous return line after each
256 dialysis session. Initiation of therapy may be prompted by trough (pre-
257 dialysis) plasma levocarnitine concentrations that are below normal
258 (40-50 μmol/L). Dose adjustments should be guided by trough (pre-
259 dialysis) levocarnitine concentrations, and downward dose
260 adjustments (e.g. to 5 mg/kg after dialysis) may be made as early as
261 the third or fourth week of therapy.

262

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

266

267 **COMPATIBILITY AND STABILITY**

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

273

274 **HOW SUPPLIED**

275 CARNITOR® (levocarnitine) Injection is available in 1 g per 5 mL
276 single dose ampoules packaged 5 ampoules per carton (NDC 54482-
277 146-09) or in 500 mg per 2.5 mL single dose ampoules packaged 5
278 ampoules per carton (NDC 54482-146-10). Made in Italy.

279

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

284

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

287

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

291

292 CARNITOR® (levocarnitine) Oral Solution is supplied in 118 mL (4 FL.
293 OZ.) multiple-unit plastic containers. The multiple-unit containers are
294 packaged 24 per case (NDC 54482-145-08). CARNITOR®
295 (levocarnitine) Oral Solution is manufactured for Sigma-Tau
296 Pharmaceuticals, Inc. by: Alpharma USPD, Inc. Baltimore, MD 21244-
297 2654 and/or Hi-Tech Pharmacal Co., Inc. Amityville, NY 11701.

298

299 Rx only.

300

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PREVIOUS EDITION IS OBSOLETE
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