

LEVOCARNITINE- levocarnitine injection
Hikma Pharmaceuticals USA Inc.

Levocarnitine Injection, USP

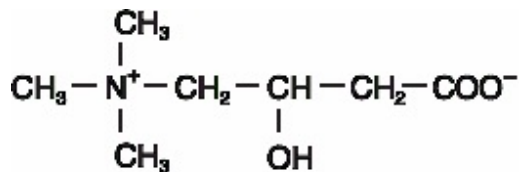
FOR INTRAVENOUS USE ONLY

Rx only

DESCRIPTION

Levocarnitine is a carrier molecule in the transport of long-chain fatty acids across the inner mitochondrial membrane.

The chemical name of levocarnitine is (R)-(3-Carboxy-2-hydroxypropyl)trimethylammonium hydroxide, 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:



Molecular Formula: $\text{C}_7\text{H}_{15}\text{NO}_3$

Molecular Weight: 161.20

Levocarnitine Injection, USP is a sterile aqueous solution containing 200 mg of levocarnitine per mL. The pH is adjusted to 6.0 to 6.5 with hydrochloric acid.

CLINICAL PHARMACOLOGY

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 levocarnitine. 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. Levocarnitine 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 accumulation 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 $\mu\text{mol/L}$ 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 Levocarnitine 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, Levocarnitine Tablets were found to be bio-equivalent to Levocarnitine Oral Solution. Following 4 days of dosing with 6 tablets of levocarnitine 330 mg b.i.d. or 2 g of levocarnitine oral solution b.i.d., the maximum plasma concentration (C_{max}) was about 80 $\mu\text{mol/L}$ 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 levocarnitine were described by a two-compartment model. Following a single i.v. administration, approximately 76% of the levocarnitine dose was excreted in urine during the 0 to 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 levocarnitine, calculated after correction for circulating endogenous plasma concentrations of levocarnitine, was $15.1 \pm 5.3\%$ for Levocarnitine Tablets and $15.9 \pm 4.9\%$ for Levocarnitine 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 levocarnitine 20 mg/kg three times per week after dialysis. Prior to initiation of levocarnitine therapy, mean plasma levocarnitine concentrations were approximately 20 $\mu\text{mol/L}$ pre-dialysis and 6 $\mu\text{mol/L}$ post-dialysis. The table summarizes the pharmacokinetic data (mean \pm SD $\mu\text{mol/L}$) after the first dose of Levocarnitine and after 8 weeks of levocarnitine 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 levocarnitine therapy (3 doses), all patients had trough concentrations between 54 and 180 µmol/L (normal 40 to 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 levocarnitine 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 levocarnitine 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 levocarnitine 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 [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 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 [³H]-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 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).

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

Hypersensitivity Reactions

Serious hypersensitivity reactions, including anaphylaxis, laryngeal edema, and bronchospasm have been reported following levocarnitine administration, mostly in patients with end stage renal disease who are undergoing dialysis. Some reactions occurred within minutes after intravenous administration of levocarnitine.

If a severe hypersensitivity reaction occurs, discontinue levocarnitine treatment and initiate appropriate medical treatment. Consider the risks and benefits of re-administering levocarnitine to individual patients following a severe reaction. If the decision is made to re-administer the product, monitor patients for a reoccurrence of signs and symptoms of a severe hypersensitivity reaction.

PRECAUTIONS

Drug Interactions

Reports of INR increase with the use of warfarin have been observed. It is recommended that INR levels be monitored in patients on warfarin therapy after the initiation of treatment with levocarnitine or after dose adjustments.

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

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 levocarnitine. 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

Clinical Trials Experience

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.

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
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
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Postmarketing Experience

The following adverse reactions have been reported:

Neurologic Reactions: Seizures have been reported to occur in patients, with or without preexisting seizure activity, receiving either oral or intravenous levocarnitine. In patients with preexisting seizure activity, an increase in seizure frequency and/or severity has been reported.

Hypersensitivity reactions: Anaphylaxis, laryngeal edema and bronchospasm (see **WARNINGS**)

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.

DOSAGE AND ADMINISTRATION

Levocarnitine Injection is administered intravenously.

Metabolic Disorders

The recommended dose is 50 mg/kg given as a slow 2 to 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 to 20 mg/kg dry body weight as a slow 2 to 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 to 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

Levocarnitine 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

Levocarnitine Injection, USP, 200 mg per 1 mL, is available in 5 mL single dose vials packaged 10 vials per carton **NDC (0143-9852-10)**.

Store vials at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]. Retain vial in carton until time of use. **Protect from light.** Discard unused portion of an opened vial, as they contain no preservative.

To report SUSPECTED ADVERSE REACTIONS, contact Hikma Pharmaceuticals USA Inc. at 1-877-845-0689, or the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. For product inquiry call 1-877-845-0689.

REFERENCES

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10. Rebouche, C.J. 1991. Quantitative estimation of absorption and degradation of a carnitine supplement by human adults. *Metabolism* 40:1305-1310.

Manufactured by:

HIKMA FARMACÊUTICA (PORTUGAL), S.A.

Estrada do Rio da Mó, 8, 8A e 8B - Fervença - 2705-906 Terrugem SNT, PORTUGAL

Distributed by:

Hikma Pharmaceuticals USA Inc.

Berkeley Heights, NJ 07922

January 2023

PIN430-WES/4

VIAL LABEL

NDC 0143-**9852**-01 Rx only

Levocarnitine Injection, USP

1 gram per 5 mL

(200 mg/mL)

For Intravenous use ONLY

5 mL Single-Dose Vial

NDC 0143-9852-01 Rx only

Levocarnitine Injection, USP

1 gram per 5 mL
(200 mg/mL)

For Intravenous use ONLY
5 mL Single-Dose Vial

Usual Dosage: See package insert. Each mL contains Levocarnitine 200 mg, pH adjusted to 6.0 to 6.5 with HCl.

Store vials at 20° to 25°C (68° to 77°F). [See USP]. Protect from freezing.

Retain vial in carton until time of use. **Protect from light.** Discard unused portion of an opened vial, as they contain no preservative.

Distributed by
Hikma Pharmaceuticals USA, Inc.
Berkley Heights, N.J. 07922

PLB971-WES4

Lot:
Exp:

CARTON LABEL

NDC 0143-**9852**-10 Rx only

Levocarnitine Injection, USP

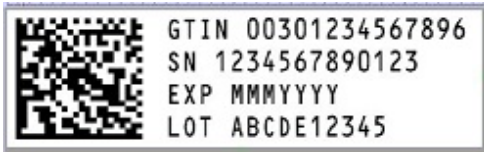
1 gram per 5 mL

(200 mg/mL)

For Intravenous use ONLY

10 x 5 mL Single-Dose Vials

SERIALIZATION IMAGE



Representative serialization image

LEVOCARNITINE

levocarnitine injection

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:0143-9852
Route of Administration	INTRAVENOUS		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
LEVOCARNITINE (UNII: 0G389FZZ9M) (LEVOCARNITINE - UNII:0G389FZZ9M)	LEVOCARNITINE	1 g in 5 mL

Inactive Ingredients

Ingredient Name	Strength
HYDROCHLORIC ACID (UNII: QTT17582CB)	
SODIUM HYDROXIDE (UNII: 55X04QC32I)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0143-9852-10	10 in 1 CARTON	06/01/2023	
1	NDC:0143-9852-01	5 mL in 1 VIAL, SINGLE-USE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA075567	06/01/2023	

Labeler - Hikma Pharmaceuticals USA Inc. (001230762)