HOSPIMAX
Maximising Life

Nefcarnit™

Levocarnitine 1 gm Injection

Prevents Carnitine Deficiency

NEFCARNIT INJECTION

Levocarnitine Injection 1 g per 5 mL Ampoule
FOR INTRAVENOUS USE ONLY.

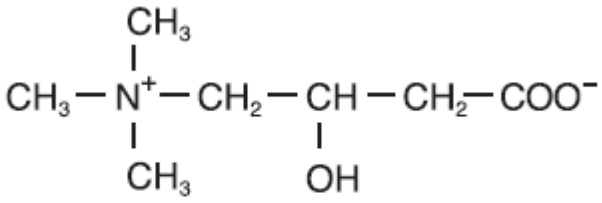
Product Description:

- Nefcarnit Injection: Each 5 ml contains Levocarnitine USP 1.0 gm

DESCRIPTION

NEFCARNIT(levocarnitine) is a carrier molecule in the transport of long-chain fatty acids across the inner mitochondrial membrane. Levocarnitine Injection USP is a sterile aqueous solution containing 1 g of levocarnitine per 5 mL ampoule.The pH is adjusted to 6.0 to 6.5 with hydrochloric acid.

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:



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

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. Levocarnitinemay 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 µmol/L at one week post term and may be associated with low tissue and/or urineconcentrations. 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 levocarnitinehave shown that administration of levocarnitine to ESRD patients on hemodialysis results in increased plasma levocarnitine concentrations.

PHARMACOKINETICS

The plasma concentration profiles of levocarnitine after a slow 3 minute intravenous bolus dose of 20 mg/kg of levocarnitinewere 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.

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].

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]

INDICATIONS AND USAGE

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

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

CONTRAINDICATIONS

None known.

WARNINGS

Hypersensitivity Reactions

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

If a severe hypersensitivity reaction occurs, discontinue levocarnitineinjectiontreatment and initiate appropriate medical treatment. Consider the risks and benefits of re-administering levocarnitineinjectionto 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

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.

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

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 inseizure frequency and/or severity has been reported.

OVERDOSAGE

There have been no reports of toxicity from levocarnitine overdosage.

Metabolic Disorders

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} oflevocarnitine in mice is 19.2 g/kg. Large doses of levocarnitine maycause diarrhea.

DOSAGE AND ADMINISTRATION

Levocarnitine Injection is administered intravenously.

ESRD Patients on Hemodialysis

The recommended starting dose is 10-20 mg/kg 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.

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.

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 is available in 1 g per 5 mL single dose ampoule packaged 5 ampoule per carton.

Store ampoules at controlled room temperature (25°C). Discard unused portion of an opened ampoule, as the formulation does not contain a preservative.

REFERENCES

1. Bohmer, T., Rydning, 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.* 17:561-568.
3. Christiansen, R., Bremer, J. 1976. Active transport of butyrobetaine and carnitine into isolated liver cells. *Biochim. Biophys. Acta* 448:562-577.
4. Lindstedt, S. and Lindstedt, G. 1961. Distribution and excretion of carnitine in the rat. *Acta Chem. 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.* 6:41-66.
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. 1991. Protein binding of L-carnitine family components. *Eur. J. Drug Met. Pharmacokin.*, Special Issue III: 364-368.
10. Rebouche, C.J. 1991. Quantitative estimation of absorption and degradation of a carnitine supplement by human adults. *Metabolism* 40:1305-1310.