

ABCARTINETM

L-Carnitine 1000mg **Injection**

DESCRIPTION ABCARTINE (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° .

Empirical Formula: C₇H₁₅NO₃ **Molecular Weight:** 161.20 Each ABCARTINE (levocarnitine) Tablet contains levocarnitine and the inactive ingredients magnesium stearate, microcrystalline cellulose and povidone.

CLINICAL PHARMACOLOGY ABCARTINE (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 ABCARTINE. 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 This label may not be the latest approved by FDA. For current labeling information, please visit <https://www.fda.gov/drugsatfda> 2 Secondary carnitine deficiency can be a consequence of inborn errors of metabolism. ABCARTINE 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 lifethreatening. 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.

PHARMACOKINETICS In a relative bioavailability study in 15 healthy adult male volunteers, ABCARTINE Tablets were found to be bio-equivalent to ABCARTINE Oral Solution. Following 4 days of dosing with 6 tablets of ABCARTINE 330 mg b.i.d. or 2 g of ABCARTINE oral solution b.i.d., 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 ABCARTINE 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 ABCARTINE, calculated after correction for circulating endogenous plasma concentrations of levocarnitine, was 15.1 ± 5.3% for ABCARTINE Tablets and 15.9 ± 4.9% for ABCARTINE 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.

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 This label may not be the latest approved by FDA. For current labeling information, please visit <https://www.fda.gov/drugsatfda> 3 After attainment of steady state following 4 days of oral administration of ABCARTINE 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 ABCARTINE (levocarnitine) 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 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. ABCARTINE (levocarnitine) is also indicated for acute and chronic treatment of patients with an inborn error of metabolism which results in a secondary carnitine deficiency.

CONTRAINDICATIONS None known.

WARNINGS None.

PRECAUTIONS 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.

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 ABCARTINE. 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.

OVERDOSAGE There have been no reports of toxicity from levocarnitine overdose. 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 ABCARTINE (levocarnitine) Tablets.

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. This label may not be the latest approved by FDA. For current labeling information, please visit <https://www.fda.gov/drugsatfda>

5 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. **ABCARTINE (levocarnitine) Oral Solution and ABCARTINE SF (levocarnitine) Sugar-Free 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 ABCARTINE (levocarnitine) Oral Solution or ABCARTINE SF (levocarnitine) Sugar-Free 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 ABCARTINE (levocarnitine) Oral Solution or ABCARTINE SF (levocarnitine) Sugar-Free 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.