L-Carnitine
Hard gelatin capsules and syrup

**Company name**
ARAB COMPANY FOR PHARMACEUTICALS & MEDICINAL PLANTS (MEPACO-MEDIFOOD)

**Trade name**
L-Carnitine

**Generic name**
L-Carnitine (as tartarate)

**Pharmaceutical form**
Hard gelatin capsules

**Composition**

**L-Carnitine capsules**
Each hard gelatin capsule contains:

**Active ingredients:**
L-carnitine (as tartarate) 350 mg

**Inactive ingredients:**
Aerosil R972 pharma, calcium phosphate dibasic anhydrous, Povidone K 25 and magnesium stearate.

**L-Carnitine syrup**
Each 100 ml contains:

**Active ingredients:**
L-Carnitine base 30 gm

**Inactive ingredients**
Sucrose, nipagen sodium, nipazole sodium, strawberry flavor, D,L Malic acid and purified water.

**Clinical Pharmacology**

L-Carnitine 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 L-Carnitine. 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.

L-Carnitine 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 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 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, 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 (Cmax) was about 80 µmol/L and the time to maximum plasma concentration (Tmax) 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 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 Levocarnitine, calculated after correction for circulating endogenous plasma concentrations of levocarnitine, was 15.1 ± 5.3% for Levocarnitine Tablets and 15.9 ± 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.

**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. 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.

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**

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

**Dosage and administration**

- **L-Carnitine capsules** are for oral use and should be swallowed whole with a glass of water.
- **L-Carnitine Oral Solution** are for oral use only (Not for parenteral use). It can be drunk directly or diluted with water or fruit juices.

**Adults:** The recommended dosage of levocarnitine is 1 to 3 g/day for a 50 kg subject, which is equivalent to 3-10 mL/day of L-Carnitine 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.

**Infants and children:** The recommended dosage of levocarnitine is 50 to 100 mg/kg/day. 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 (10 mL/day) while assessing tolerance and therapeutic response. Monitoring should include periodic blood chemistries, vital signs, plasma carnitine concentrations, and overall clinical condition. 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.

**Contraindications**

None known

**Warnings**

None

**Precautions**

**General**

L-Carnitine oral solution is for oral/internal use only.

**Not for parenteral use.**

Gastrointestinal reactions may result from a too rapid consumption of carnitine. L-Carnitine (levocarnitine) 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. 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**
No long-term animal studies have been performed to evaluate the carcinogenic potential of levocarnitine.

**Pregnancy**
**Pregnancy Category B.**

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.
Consideration may be given to discontinuation of nursing or of levocarnitine treatment.

**Pediatric Use**
See Dosage and Administration.

**Adverse reactions**
Various mild gastrointestinal complaints have been reported during the long-term administration of oral,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 L-Carnitine (levocarnitine) Oral Solution 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.

**Package and storage**
A carton box containing 2 strips (Al-PVC) each of 10 capsules and inner leaflet.
A carton box containing a 30 ml brown bottle and inner leaflet.
Store in a dry place at temperature not exceeding 30˚ C.