Summary of Product Characteristics for

Levocarnitine Injection USP 1g/5ml

1. Name of the medicinal product
Levocarnitine Injection USP 1g/5ml

2. Qualitative and quantitative composition
Each 5ml Ampoule contains:
Levocarnitine USP.... 1g

3. Pharmaceutical form
Sterile clear colorless aqueous solution for injection

4. Clinical particulars
4.1 Therapeutic indications

For 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 (ESRD) who are undergoing dialysis.

4.2 Posology and method of administration
Levocarnitine Injection is administered intravenously.
Metabolic Disorders

The recommended dose is 50 mg/kg given as a slow 2-3 minute bolus injection or by infusion. Mostly, 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 every three hours or every four hours, and never less than every six hours, either by infusion or by intravenous injection. Following 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. Monthly and weekly observation is recommended as well. This observation should include vital signs, plasma carnitine concentrations (the plasma free carnitine concentration should be between 35 and 60 μmol/L), blood chemistries and overall clinical condition.

ESRD Patients on Hemodialysis

After each dialysis session, the suggested initial dose is 10-20 mg/kg dry body weight as a slow 2-3 minute bolus injection into the venous return line. 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. For particulate matter and discoloration, parenteral drug products should be inspected visually prior to administration, whenever container and solution permit.

4.3 Contraindications

None known

4.4 Special warnings and precautions for use

Hypersensitivity Reactions

Laryngeal edema, bronchospasm and anaphylaxis are serious hypersensitivity reactions, have been reported after levocarnitine administration, mostly in patients with end stage renal disease who are undergoing dialysis. Some reactions occurred within minutes after intravenous administration of levocarnitine. Discontinue levocarnitine treatment if a severe hypersensitivity reaction occurs and initiate appropriate medical treatment. Following a severe reaction, consider the benefits and risks of re-administering levocarnitine to individual patients. Monitor patients for a re-occurrence of signs and symptoms of a severe hypersensitivity reaction, if decision is made to re-administer the product.

General Precautions

In patients with renal insufficiency, the safety and efficacy of oral levocarnitine has not been evaluated. 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.

4.5 Interaction with other medicinal products and other forms of interaction

There have been very rare reports of International Normalised Ratio (INR) increased in patients treated concomitantly with levocarnitine and coumarinic drugs. INR or other appropriate test of coagulation should be checked weekly in patients taking anticoagulants such as warfarin along with levocarnitine, until they become stable and monthly thereafter.

4.6 Fertility, pregnancy and lactation

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.

However, there are no adequate and well controlled studies in pregnant women. As 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 levocarnitine treatment or of nursing.

4.7 Undesirable effects

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.

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

Postmarketing Experience

The following adverse reactions have been reported:

Neurologic Reactions: Seizures have been reported to occur in patients, with or without pre-existing 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

4.8 Overdose

No reports of toxicity from levocarnitine overdosage have been observed. Levocarnitine is easily removed from plasma by dialysis. The intravenous LD50 of levocarnitine in rats is 5.4 g/kg. Large doses of levocarnitine may cause diarrhea.

5. Pharmacological properties

5.1 Pharmacodynamic properties

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. Fatty acids are the main substrate for energy production, in skeletal and cardiac muscle.

5.2 Pharmacokinetic properties

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

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 IV 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.

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 80µmol/L and the time to maximum plasma concentration (Tmax) occurred at 3.3 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.

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 was approximately 20µmol/L pre-dialysis and 6 µmol/L post-dialysis. The table summarizes the pharmacokinetic data (mean ± SD µmol/L) after the first dose of levocarnitine and after 8 weeks of levocarnitine therapy.

N=12	Baseline	Single dose	8 weeks
Cmax	-	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 40-50 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 [^{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.

After reaching 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).

5.3 Preclinical safety data

Mutagenesis, Carcinogenesis, and Impairment of Fertility

No long-term animal studies have been performed to evaluate the carcinogenic potential of levocarnitine. Mutagenicity tests performed in *Schizosaccharomyces pombe*, *Saccharomyces cerevisiae* and *Salmonella typhimurium* indicate that levocarnitine is not mutagenic.

6. Pharmaceutical particulars

6.1 List of excipients

Hydrochloric acid USP
Water for injection USP

6.2 Incompatibilities

Not known.
Levocarnitine Injection is compatible and stable when mixed in parenteral solutions of 0.9% sodium chloride 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.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store below 30°C, Protect from light, avoid excessive heat.

6.5 Nature and contents of container

Levocarnitine injection is supplied in a 5ml transparent glass ampoule with OPC Red Dot.

6.6 Special precautions for disposal and other handling

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Discard unused portion of an opened vial, as the formulation does not contain a preservative.

7. Marketing authorisation holder

Samrudh pharmaceuticals pvt.ltd
A/101, Prarthana Apt. Plot No. 15, Jawahar Nagar, S. V. Road, Goregaon (W), Mumbai - 400 062

Manufacturing address.

Samrudh pharmaceuticals pvt.ltd
A/101, Prarthana Apt. Plot No. 15, Jawahar Nagar, S. V. Road, Goregaon (W), Mumbai - 400 062

8. Marketing authorisation number(s)
H2024/CTD8934/19838

9. Date of first authorisation/renewal of the authorisation
23/02/2024.

10. Date of revision of the text
November 2024.