
CARNISURE SYRUP

1. Generic Name

Levocarnitine Oral Solution U.S.P.

2. Qualitative and quantitative Composition:

Each 5 ml contains:

Levocarnitine I.P. 500 mg

Flavoured Syrupy Baseq.s.

Colour: Carmoisineq.s

The list of excipients used are Sugar, Malic Acid, Propyl Paraben, Carmosine, Methyl Paraben.

3. Dosage form and strength

Dosage form: Syrup

Strength: 500 mg/5ml

4. Clinical particulars

4.1. Therapeutic indication

It is indicated for the treatment of carnitine deficiency.

4.2. Posology and method of administration

Posology

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 levocarnitine 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 levocarnitine 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. Monitoring should include periodic blood chemistries, vital signs, plasma carnitine concentrations, and overall clinical condition.

Levocarnitine oral solution may be consumed alone or dissolved in drink or other liquid food. Doses should be spaced evenly throughout the day (every three or four hours) preferably during or following meals and should be consumed slowly to maximize tolerance).

Method of administration

For oral use only. Not for parenteral use.

4.3. Contraindications

None known

4.4. Special warnings and precautions for use

Hypersensitivity Reactions

Serious hypersensitivity reactions, including rash, urticaria, and facial edema have been reported with oral levocarnitine. Other serious hypersensitivity reactions, including anaphylaxis, laryngeal edema, and bronchospasm have been reported following intravenous levocarnitine administration, mostly in patients with end-stage renal disease undergoing dialysis.

Discontinue use of levocarnitine and instruct patients to seek medical attention if they experience symptoms suggestive of a hypersensitivity reaction.

General

Levocarnitine oral solution is for oral/internal use only. Not for parenteral use.

Gastrointestinal reactions may result from a too rapid consumption of carnitine. Levocarnitine oral solution may be consumed alone or dissolved in drinks or other liquid foods to reduce taste fatigue. They should be consumed slowly, and doses should be spaced evenly throughout the day to maximize tolerance.

The safety and efficacy of oral levocarnitine have 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.

4.5. Drugs 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.

4.6. Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Pregnancy

Reproductive studies have been performed in rats and rabbits at doses up to 3.8 times the human dose based on 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.

4.7. Effects on ability to drive and use machines

There are no data the effect of this product on driving capacity and use of machines. An effect is, however, unlikely.

4.8. Undesirable effects

The following adverse reactions associated with the use of oral formulations of levocarnitine were identified in clinical trials or post marketing reports. Because these reactions were reported voluntarily from a population of uncertain size, it is not always possible to estimate their frequency, reliability, or to establish a causal relationship to drug exposure.

Gastrointestinal Reactions:

Various mild gastrointestinal complaints have been reported during the long-term administration of oral L- or D, L-carnitine; these include transient nausea and vomiting, abdominal cramps, and diarrhea. Gastrointestinal adverse reactions with levocarnitine oral solution dissolved in liquids 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.

Musculoskeletal Reactions:

Mild myasthenia has been described only in uremic patients receiving D, L-carnitine.

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 pre-existing seizure activity, an increase in seizure frequency and/or severity has been reported.

Hypersensitivity Reactions:

Rash, urticaria, and facial edema have been reported with oral levocarnitine.

Reporting of adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Report suspected adverse reactions via any point of contact available at www.torrentpharma.com.

4.9. Overdose

There have been no reports of toxicity from levocarnitine overdosage. Levocarnitine is easily removed from plasma by dialysis. The intravenous LD of levocarnitine in rats is 5.4 g/kg and the oral LD of levocarnitine in mice is 19.2 g/kg. Large doses of levocarnitine may cause diarrhea.

5. Pharmacological properties

5.1. Mechanism of Action

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.

5.2. Pharmacodynamic properties

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.

Secondary carnitine deficiency can be a consequence of inborn errors of metabolism. 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 acyl-CoA dehydrogenase deficiency. Autointoxication occurs in these patients due to the accumulation of acyl-CoA compounds that disrupt intermediary metabolism. The subsequent hydrolysis of the acyl-CoA compound to its free acid results in acidosis which can be life-threatening. Levocarnitine clears the acyl CoA 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.

5.3. Pharmacokinetic properties

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 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 $15.1 \pm 5.3\%$ 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.

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).

6. Nonclinical properties

6.1. Animal Toxicology or Pharmacology

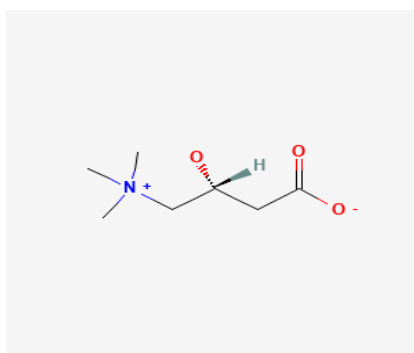
Carcinogenesis, Mutagenesis, Impairment of Fertility

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.

7. Description

Levocarnitine:

Levocarnitine is (R) -3- Carboxy-2-hydroxy-N,N,N-trimethyl -1-propanaminium, inner salt; (R) -3- Carboxy-2-hydroxypropyl)trimethylammonium, inner salt. The empirical formula is $C_7H_{15}NO_3$ and its molecular weight is 161.20 g/mol. The chemical structure of Levocarnitine is:



Carnisure Syrup

Carnisure Syrup is red coloured, clear, flavoured liquid. The list of excipients used are Sugar, Malic Acid, Propyl Paraben, Carmosine, Methyl Paraben.

8. Pharmaceutical particulars

8.1. Incompatibilities

Not applicable

8.2. Shelf-life

Do not use later than the date of expiry.

8.3. Packaging information

Carnisure Syrup is available in 30 ml Bottle.

8.4. Storage and handing instructions

Store in a cool place.

For paediatric use only

Keep out of reach of children.

Shake well before use.

Keep the bottle well closed after each use.

9. Patient Counselling Information

Ask the patients to inform the treating physicians in case of any of the below:

- Have any allergies
- Have kidney or liver problems
- Are pregnant or plan to become pregnant
- Are breastfeeding or plan to breastfeed
- Have any serious illness
- Are taking any medicines (prescription, over-the-counter, vitamins, or herbal products)

10. Details of manufacturer

Akums Drugs & Pharmaceuticals Ltd.

Plot No.: 22, Sector -6A,

I.I.E, SIDCUL, Ranipur,

Haridwar-249403.

11. Details of permission or licence number with date

Mfg Lic No. 123/UA/2007 issued on 16.09.2019

12. Date of revision

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IN/CARNISURE SYRUP/MAR-2026/02/PI