SUMMARY OF PRODUCT CHARACTERISTICS

1. Proprietary name

CARNITENE 1 g/5 mL solution for injection for intravenous use
CARNITENE 2 g/5 mL solution for injection for intravenous use
CARNITENE 1 g/10mL oral solution
CARNITENE 2 g/10mL oral solution
CARNITENE 1.5 g/5 mL oral solution
CARNITENE 1 g chewable tablets
CARNITENE 1 g/100 mL solution for infusion with sodium chloride
CARNITENE 2,5 g/250 mL solution for infusion with sodium chloride
CARNITENE 1 g/100 mL solution for infusion with glucose
CARNITENE 2,5 g/250 mL solution for infusion with glucose

2. Qualitative and quantitative composition

CARNITENE 1 g/5 mL solution for injection for intravenous use
One ampoule contains:
active ingredient: L-carnitine inner salt 1.00 g

CARNITENE 2 g/5 mL solution for injection for intravenous use
One ampoule contains:
active ingredient: L-carnitine inner salt 2.00 g

CARNITENE 1g/10mL oral solution
One single-dose vial contains:
active ingredient: L-carnitine inner salt 1.00 g

CARNITENE 2g/10mL oral solution
One single-dose vial contains:
active ingredient: L-carnitine inner salt 2.00 g

CARNITENE 1.5 g/5 mL oral solution
100 mL of solution contain:
active ingredient: L-carnitine inner salt 30 g

CARNITENE 1g chewable tablets
One chewable tablet contains:
active ingredient: L-carnitine inner salt 1.00 g

CARNITENE 1 g/100 mL solution for infusion with sodium chloride
One bag contains: active ingredient: L-carnitine inner salt g 1.00

CARNITENE 2,5 g/250 mL solution for infusion with sodium chloride
One bag contains: active ingredient: L-carnitine inner salt g 2.50

CARNITENE 1 g/100 mL solution for infusion with glucose
One bag contains: active ingredient: L-carnitine inner salt g 1.00

CARNITENE 2,5 g/250 mL solution for infusion with glucose
One bag contains: active ingredient: L-carnitine inner salt g 2.50

Excipients are listed under point 6.1

3. Pharmaceutical forms

Solution for injection, oral solution, chewable tablets, solution for infusion.

4. Clinical information

4.1 Therapeutic indications

Primary and secondary carnitine deficiencies.

4.2 Dosage and administration

oral solution - chewable tablets:

Primary carnitine deficiencies and deficiencies secondary to inborn errors:

The recommended daily oral dose depends on age and body weight: from 0 to 2 years 150 mg/kg b.w.; from 2 to 6 years 100 mg/kg b.w.; from 6 to 12 years 75 mg/kg b.w.; over 12 years and in adults 2-4 g according to the severity of pathology and the physician's opinion.

Secondary carnitine deficiency due to haemodialysis:

2-4 g/day.

The oral solutions must be taken only after dilution. The content of the single-dose vial must be diluted in a glass of water.

Solution for injection for intravenous use – Solution for infusion:

Secondary deficiency due to haemodialysis

2 g at the end of the dialytic session, administered by slow intravenous infusion.

The 2.5 g dosage may be indicated in patients in dialysis for more than 1 year.

5 ml vials

Intravenous administration should be performed slowly (2-3 minutes).

Bags of 100 ml and 250 ml

The infusion should be administered at 3 ml per minute rate, corresponding to approximately 30 minutes for 100 ml bags and 1 hour and 20 minutes for 250 ml bags.

4.3 Contraindications

Hypersensitivity to the active ingredient or to any of the excipients.

The solution for infusion with sodium chloride is contraindicated in patients with ipernatremia and plethora idrosaline.

The solution for infusion with glucose is contraindicated in diabetic patients.

4.4 Special precautions

Since L-carnitine improves glucose utilization, the administration of L-carnitine to diabetic patients receiving either insulin or hypoglycemic oral treatment may result in hypoglycemia. Plasma glucose levels in these subjects must therefore be regularly monitored in order to enable an immediate adjustment of the hypoglycemic treatment.

Intravenous administration must be slow (2-3 minutes).

CARNITENE solution for infusion should be used with great caution in patients with congestive heart failure, severe renal insufficiency and in clinical states in which there exists oedema with salt retention, in patients treated with corticosteroid or corticotropinic drugs. The continuous administration without the addition of potassium may cause ipokalemia.

The balance of fluids and electrolytes must be monitored.

Safety and efficacy of levocarnitine for oral administration have not been shown in patients with renal failure. Chronic oral administration of high doses of levocarnitine in patients with severe renal dysfunction or with end stage renal disease (ESRD) and undergoing dialysis may induce accumulation of the potentially toxic metabolites trimethylamine (TMA) and trimethylamine-N-oxide (TMAO), since these metabolites are normally excreted in the urine.

This event does not occur with intravenous administration (see 5.2).

L-carnitine is a physiological product and therefore shows no risk of addiction or dependence.

Both the oral solution (1.5g/5mL – 20ml bottle) and the chewable tablets contain sucrose: these drugs should be used with caution in patients with rare fructose intolerance hereditary problems, glucose-galactose malabsorption, or sucrase-isomaltase deficiency.
Moreover, this must also be considered in diabetic patients and in patients who are placed in a hypocaloric diet regimen.
The oral solution (1.5 g / 5 ml - 20 ml bottle) also contains sorbitol: this product should be used with caution in patients with rare fructose intolerance inherited problems.
The oral solution (1.5 g / 5 ml - 20 ml bottle) contains also para-hydroxy-benzoates as preservatives: these may cause allergic reactions (delayed onesincluded)

4.5 Interactions with other drugs and substances
No interactions between L-carnitine and other drugs are known.

4.6 Pregnancy and breast feeding
The drug can be used both during pregnancy and breast feeding.

4.7 Effects on driving and operating machinery
L-Carnitine does not affect the ability to drive or operate machinery.

4.8 Adverse drug reactions
Slight gastrointestinal disorders after oral administration have been shown. In uremic patients mild symptoms of myasthenia have been reported.
Cases of seizures have been reported to occur in patients with or without pre-existing seizure activity, after receiving either oral or intravenous L-carnitine.

4.9 Overdosage
No toxic effects due to overdosage of L-carnitine have been reported.

5. Pharmacological characteristics

5.1 Pharmacodynamic characteristics
Pharmacotherapeutic category: mitochondrial agonist.
ATC: A16AA01
Carnitine is a natural component of the cell where it plays an essential role in energy production and transport.
In fact, Carnitine is the only carrier used by long chain fatty acids both to cross the internal mitochondrial membrane, and to lead towards beta-oxidation; moreover L-carnitine controls the transport of the mitochondrial energy to the cytoplasma by modulating the adenine-nucleotide-translocase enzyme.
The highest carnitine tissue concentration is found in skeletal muscles and myocardium; although the latter is able to use various substrates for energy production, it normally uses fatty acids.
Carnitine therefore plays an essential role in the cardiac metabolism, since the oxidation of fatty acids strictly depends on the presence of an adequate amount of the substance.
Experimental studies have shown that in several conditions such as stress, acute ischemia and diphtheric myocarditis, a decrease of Carnitine levels in myocardial tissues can be shown. Many animal models have confirmed a positive activity of Carnitine in a variety of induced heart disfunctions: acute and chronic ischemia, cardiac decompensation, cardiac insufficiency due to diphtheritic myocarditis, drug-induced cardiotoxicity (propranolol, adriamycin).
L-carnitine has shown therapeutic activity in the following pathologies:

a) primary carnitine deficiencies characterized by phenotypes such as myopathies with lipidic accumulation, Reye's syndrome-type hepatic encephalopathy and/or progressive dilatative cardiomyopathy.
b) secondary carnitine deficiencies in patients with genetic organic acidurias such as propyonic acidemia, methyl-malonic aciduria, isovaleric acidemia and in patients with genetic beta-oxidation defects. In these situations the secondary carnitine deficiency shows as esters with

fatty acids. In fact, endogenous L-carnitine acts as a “buffer” for fatty acids that cannot be metabolized.

c) secondary carnitine deficiencies in patients undergoing intermittent hemodialysis. Muscular depletion of L-carnitine is directly related to the loss of this substance in the dialysis fluid.
The muscular symptoms typically seen in these patients after the dyalitic session, have been shown to be improved with the exogenous treatment.

5.2 Pharmacokinetic characteristics

L-carnitine, administered intravenously, is eliminated mainly by renal route. The metabolic component is purely marginal with the exception of the reversible transformation of L-carnitine in its esters.
On the contrary, after oral administration, L-carnitine is degraded by the intestinal bacteria to trimethylamine (TMA) and gamma-butyrobetaine. Since the amount of the drug that reaches unchanged the systemic circulation is approximately 10-20%, it is estimated that the intestinal metabolism is responsible for the elimination of approximately 80-90% of an oral dose of L-carnitine.
The products of the intestinal metabolism, gamma-butyrobetaine and TMA are both absorbed. Gamma-butyrobetaine is found unchanged in the urine while TMA is transformed by hepatic metabolism in trimethylamine-N-oxide (TMAO) that is found in the urine together with small quantities of unchanged TMA.
Chronic oral administration of L-carnitine in patients with severe renal impairment or undergoing dialysis may cause accumulation of TMA and TMAO in the blood with subsequent trimethylaminuria, a pathological condition characterized by a strong "fish odour" of urine, breath and sweat of the patient.

5.3 Pre-clinical safety data

Acute toxicology studies on rats and on *Mus musculus* for 7 days have established an LD_{50} of >8000 mg/kg by oral route and of 4000 mg/kg by i.v. route.
Research on rats and dogs with a 12 months consecutive oral treatment have determined no cases of death nor significant alterations of function and histological structure of principal organs. Teratogenesis studies have shown that L-carnitine does not have damaging effects on the pregnant female, on gestation or on embryo-fetal development.

6. Pharmaceutical information

6.1 List of the inactive ingredients

solution for injection for intravenous use
water for injection

1g/10mL oral solution
d-l malic acid, sodium benzoate, sodium saccharinate, purified water.

2g/10mL oral solution
d-l malic acid, sodium benzoate, sodium saccharinate, pineapple aroma powder, purified water.

1.5 g/5 mL oral solution
sucrose, 70%-sorbitol solution (not crystallizable), sodium methyl p-hydroxybenzoate, sodium propyl p-hydroxybenzoate, cherry aroma, black cherry aroma, purified water.

chewable tablets:
mint aroma powder, licorice aroma powder, sucrose, magnesium stearate

solution for infusion with sodium chloride
sodium chloride, diluted hydrochloric acid, water for injection

solution for infusion with glucose
glucose monohydrate, water for injection

6.2 Incompatibility

No incompatibility of L-carnitine with other drugs is known.

6.3 Shelf-life

CARNITENE 1 g/5 mL solution for injection for intravenous use: 4 years
CARNITENE 2 g/5 mL solution for injection for intravenous use: 3 years
CARNITENE 1 g/10mL oral solution: 5 years
CARNITENE 2 g/10mL oral solution: 3 years
CARNITENE 1.5 g/5 mL oral solution: 5 years
CARNITENE 1 g chewable tablets: 3 years
CARNITENE 1 g/100 mL solution for infusion with sodium chloride: 2 years
CARNITENE 2.5 g/250 mL solution for infusion with sodium chloride: 2 years
CARNITENE 1 g/100 mL solution for infusion with glucose: 1 year
CARNITENE 2.5 g/250 mL solution for infusion with glucose: 1 year

6.4 Special precautions for storage

No special precautions are required for storage.
Solution for infusion with glucose: do not store above 25°C

6.5 Packaging

CARNITENE 1 g/5 mL solution for injection for intravenous use:
package of 5 amber glass ampoules of 5 mL
CARNITENE 2 g/5 mL solution for injection for intravenous use:
package of 5 amber glass ampoules of 5 mL
CARNITENE 1 g/10mL oral solution:
package of 10 single-dose vials of 10 mL
CARNITENE 2 g/10mL oral solution:
package of 10 single-dose vials of 10 mL
CARNITENE 1 g chewable tablets: 10 chewable tablets in blister
CARNITENE 1.5 g/5 mL oral solution:
package of 20 mL amber glass bottle
CARNITENE 1 g/100 mL solution for infusion with sodium chloride:
PVC bag with tube, polycarbonate sealed "vial", with butyl chlorine rubber stopper and aluminium ring
CARNITENE 2.5 g/250 mL solution for infusion with sodium chloride
PVC bag with tube, polycarbonate sealed "vial", with butyl chlorine rubber stopper and aluminium ring
CARNITENE 1 g/100 mL glucose solution for infusion with glucose:
PVC bag with tube, polycarbonate sealed "vial", with butyl chlorine rubber stopper and aluminium ring
CARNITENE 2.5 g/250 mL glucose solution for infusion with glucose:
PVC bag with tube, polycarbonate sealed "vial", with butyl chlorine rubber stopper and aluminium ring

It may be possible that not all the pack sizes are marketed.

6.6 Instructions for use

Any unused product or waste materials derived from such medicinal product must be disposed of in accordance with local requirements.

7. Name and address of the marketing authorization holder

Sigma-Tau Industrie Farmaceutiche Riunite S.p.A.
Viale Shakespeare, 47 – 00144 Rome, Italy

8. Marketing authorization number

CARNITENE 1 g/5 mL solution for injection for intravenous use- 5 ampoules of 5mL	MA nr. 018610028
CARNITENE 2 g/5 mL solution for injection for intravenous use - 5 ampoules of 5mL	MA nr. 018610093
CARNITENE 1 g/10mL oral solution - 10 single-dose vials of 10 mL	MA nr. 018610042
CARNITENE 2 g/10mL oral solution - 10 single-dose vials of 10 mL	MA nr. 018610079
CARNITENE 1.5 g/5 mL oral solution – 20 mL bottle	MA nr. 018610016
CARNITENE 1 g chewable tablets – 10 tablets	MA nr. 018610067
CARNITENE 1 g/100 mL solution for infusion with sodium chloride – 100 mL bag	MA nr. 018610105
CARNITENE 2.5 g/250 mL solution for infusion with sodium chloride – 250 mL bag	MA nr. 018610117
CARNITENE 1 g/100 mL solution for infusion with glucose – 100 mL bag	MA nr. 018610131
CARNITENE 2.5 g/250 mL solution for infusion with glucose – 250 mL bag	MA nr. 018610143

9. Date of first marketing authorization/ licence renewal

Authorization:

CARNITENE 1 g/5mL solution for injection for intravenous use	June 1979
CARNITENE 2 g/5mL solution for injection for intravenous use	March 1993
CARNITENE 1 g/10mL oral solution	May 1982
CARNITENE 2 g/10mL oral solution	March 1993
CARNITENE 1.5 g/5 mL oral solution	September 1969
CARNITENE 1 g chewable tablets	July 1984
CARNITENE 1 g/100 mL solution for infusion with sodium chloride	May 2007
CARNITENE 2.5 g/250 mL solution for infusion with sodium chloride	May 2007
CARNITENE 1 g/100 mL solution for infusion with glucose	June 2011
CARNITENE 2.5 g/250 mL solution for infusion with glucose	June 2011

Renewal: June 2010

10. Date of text revision

June 2011

11. Category according to law DPR 309/90

Not subject to the above law.

12. Distribution to the public

CARNITENE 2 g/10mL oral solution , CARNITENE 1g/5 mL - CARNITENE 2g/5 mL solution for injection for intravenous use
To be sold upon medical prescription

CARNITENE 1g g/10mL oral solution, CARNITENE 1 g chewable tablets, CARNITENE 1.5 g/5 mL oral solution
Not subject to medical prescription.

CARNITENE 1 g/100 mL solution for infusion with sodium chloride , CARNITENE 2.5 g/250 mL solution for infusion with sodium chloride, CARNITENE 1 g/100 mL solution for infusion with glucose, CARNITENE 2.5 g/250 mL solution for infusion with glucose
Subject to restricted medical prescription, for hospital use only.