SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

CARNITINE SOLUTION 30%

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of Carnitine Solution 30% contains 300 mg of L-Carnitine.

One bottle of 20 ml of Carnitine Solution 30% contains:
Active Ingredient: L-Carnitine 6 g.

Excipients with known effect:
Sorbitol content: 1.4 g per 20 ml solution.
Sucrose content: 0.56 g per 20 ml solution.
Sodium content: 0.00375 g per 20 ml solution.
Sodium methyl-p-hydroxybenzoate 0.02 g per 20 ml solution
Sodium propyl-p-hydroxybenzoate 0.0098 g per 20 ml solution
Ethanol 0.104 g per 20 ml solution.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Oral solution.
Clear liquid, colourless to slightly yellow solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Systemic and myopathic carnitine deficiency.

4.2 Posology and method of administration

Adults

Give 1 to 3 g/day in 2 or 3 divided doses for a 50 kg subject . Use higher doses with caution and only where clinical and biochemical considerations make it seem likely that higher doses will be of benefit.. Start dosage at 1 g/day, and increase slowly while assessing tolerance and response. Monitoring should include periodic blood chemistries, vital signs, plasma carnitine concentrations, and overall clinical condition.

Children

50 to 100 mg/kg/day. Give higher doses with caution and only where clinical and biochemical considerations make it seem likely that higher doses will be of benefit. Start dosage at 50 mg/kg/day, and increase slowly to a maximum of 3 g/day while assessing tolerance and therapeutic response. Monitoring should include periodic blood chemistries, vital signs, plasma carnitine concentrations, and overall clinical condition.
Give alone or dissolve in drinks or liquid food. Space doses evenly (every 3 or 4 hours), preferably with or after meals; consume slowly to maximize tolerance.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Since L-carnitine improves glucose utilization, the administration of L-carnitine to diabetic patients receiving either insulin or hypoglycaemic oral treatment may result in hypoglycaemia. Plasma glucose levels in these subjects must therefore be regularly monitored in order to enable an immediate adjustment of the hypoglycaemic treatment.
The balance of fluids and electrolytes must be monitored.
In patients with previous seizure activity, L-carnitine administration may increase the incidence and/or severity of seizure attacks. In patients with underling predisposing conditions, treatment with L-carnitine may trigger the convulsive crisis.
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.
L-carnitine is a physiological product and therefore shows no risk of addiction or dependence.

Very rare cases of increased INR (International Normalized Ratio) have been reported in patients treated concomitantly with coumarin drugs (see sections 4.8 and 4.5). In patients taking anticoagulants together with CARNITINE, the INR - or other suitable coagulation tests - should be checked weekly until stable values are reached and thereafter monthly.
CARNITINE SOLUTION 30% contains sucrose: patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption, or sucrase-isomaltase insufficiency should not take this medicine. May be harmful to the teeth.
Moreover, this must also be considered in diabetic patients and in patients who are placed in a hypocaloric diet regimen.
CARNITINE SOLUTION 30% contains sorbitol. Patients with rare hereditary problems of fructose intolerance should not take this medicine.
CARNITINE SOLUTION 30% contains para-hydroxy-benzoates (methyl para-hydroxy-benzoates and propyl para-hydroxy-benzoates) as preservatives: these may cause allergic reactions (possibly delayed).

4.5 Interaction with other medicinal products and other forms of interaction

Interaction between L-carnitine and coumarin drugs cannot be excluded.
Very rare cases of increased INR (International Normalized Ratio) have been reported in patients treated concomitantly with coumarin drugs (see sections 4.8 and 4.4).
The INR – or other appropriate coagulation tests – should be checked weekly until they become stable, and then monthly in patients taking anticoagulants together with CARNITINE SOLUTION 30% (see section 4.4).

Concomitant administration of CARNITINE SOLUTION 30% with drugs that induce hypocarnitaemia due to increased loss of renal carnitine (valproic acid, prodrugs containing pivalic acid, cephalosporins, cisplatin, carboplatin and ifosfamide) may reduce the availability of L-carnitine.

4.6 Fertility, pregnancy and lactation

Fertility
Favourable effects and no safety issues have been identified in clinical studies conducted on fertility.

Pregnancy
Reproduction studies were conducted in rats and rabbits. There was no evidence of a teratogenic effect in either species. In the rabbit, but not in the rat, there was more, not statistically significant, post-implantation losses at the maximum dose tested (600mg/kg per day) compared to the control group. The significance of these findings in humans is unknown.

No appropriate clinical trials have been performed in pregnant women.

CARNITINE Solution 30% should be administered during pregnancy if the benefit to the mother outweighs the potential risk to the foetus.

Lactation

L-carnitine is a normal component of human milk. The use of L-carnitine supplementation in nursing mothers has not been studied.

CARNITINE SOLUTION 30% should be used by the breast-feeding mother if the benefit to the mother outweighs any potential risk to the baby due to excessive exposure to carnitine.

4.7 Effects on ability to drive and use machines

CARNITINE SOLUTION 30% has no influence on the ability to drive and use machines.

4.8 Undesirable effects

Adverse reactions from all sources (*clinical trials, literature and post-marketing*) are listed in the following table based on the classification of Systems and Organs Class by MedDRA. Within class grouping, adverse reactions are ranked by frequency. Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness. In addition, the frequency category corresponding to any adverse reactions is based on the following convention (CIOMS III): Very common (≥ 1/10), common (≥ 1/100, <1/10), uncommon (≥ 1/1,000, <1/100), rare (≥ 1/10, 000 to <1/1, 000) very rare (<1/10, 000), frequency not known (can not be estimated from the available data).

Nervous System Disorders	
Uncommon:	Headache
Not known:	Convulsions *, dizziness
Cardiac disorders	
Not known:	Palpitations
Vascular disorders	
Uncommon:	Hypertension, hypotension
Respiratory, thoracic and mediastinal disorders	
Not known:	Dyspnea
Gastrointestinal Disorders	
Common:	Vomiting, nausea, diarrhoea, abdominal pain
Uncommon:	Dysgeusia, dyspepsia, dry mouth
Skin and subcutaneous tissue disorders	
Uncommon:	Skin odour abnormal **
Not known:	Pruritus, rash
Musculoskeletal and connective tissue disorders	
Uncommon:	Muscle spasms
Not known:	Myasthenia***, muscle tightness
Systemic disorders and administration site conditions	
Uncommon:	Chest pain, feeling abnormal, pyrexia

Diagnostic tests	
Uncommon:	Blood pressure increased
Very rare:	Increased INR****

* Seizures have been reported in patients, with or without a history of seizure activity, who receive L-carnitine orally. L-carnitine administration may increase the incidence and/or severity of seizure attacks. In patients with underling predisposing conditions, treatment with L-carnitine could trigger convulsive crisis.
** Mild myasthenic symptoms have been reported in uremic patients.
*** In subjects with renal impairment or on dialysis, chronic oral administration of L-carnitine may cause accumulation of TMA and TMAO in the blood with consequent trimethylaminuria, pathological condition characterized by a strong "fishy odor" present in urine, in the breath and sweat of the patient (see section 5.2 "Pharmacokinetic properties")
**** Very rare cases of increased INR (International Normalized Ratio) have been reported in patients treated concomitantly with coumarin drugs (see sections 4.4 and 4.5).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form http://sideeffects.health.gov.il

4.9 Overdose

High doses and long-term administration of L-carnitine have been associated with diarrhoea. L-carnitine is readily removed from the blood by dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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 cytoplasm 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 dysfunctions: 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 propionic 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 haemodialysis. 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 dialytic session, have been shown to be improved with the exogenous treatment.

5.2 Pharmacokinetic properties

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 Preclinical 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.
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-foetal development.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sorbitol 70%-solution, sucrose, sodium methyl p-hydroxybenzoate, sodium propyl p-hydroxybenzoate, colourless cherry flavour (contains ethanol) , colourless Sour black cherry flavour (contains ethanol), tartaric acid (for pH adjustment), purified water.

6.2 Incompatibilities

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

6.3 Shelf life

The expiry date of the product is indicated on the packaging material. The product must be used within a period of 15 days after first opening.

6.4 Special precautions for storage

Store in a cool place. Do not freeze.

6.5 Nature and contents of container

Carnitine solution 30%:
Package of 20 mL Type III soda–lime yellow glass, with child proof cap.

6.6 Special precautions for disposal and other handling

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

7. LICENCE HOLDER AND MANUFACTURER

Licence holder:
Teva Israel Ltd.,
124 Dvora HaNevi'a St, Tel Aviv 6944020 Israel

Manufacturer:
Alfasigma S.p.A., Bologna, Italy.

8. REGISTRATION NUMBER:

119 07.23815

The leaflet was revised in November 2023 according to MOH guidelines.