SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Carnitor 1 g Oral Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Levocarnitine 1.0 g

Excipients with known effect: each ml contains sodium methyl hydroxybenzoate (1.2 mg), sodium propyl hydroxybenzoate (0.1 mg).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Clear, colourless or light straw- coloured solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Indicated for the treatment of primary and secondary carnitine deficiency in adults and children over 12 years of age.

4.2 Posology and method of administration

Posology

Adults and children over 12 years of age
It is advisable to monitor therapy by measuring free and acyl carnitine levels in both plasma and urine.

The management of inborn errors of metabolism

The dosage required depends upon the specific inborn error of metabolism concerned and the severity of presentation at the time of treatment. However, the following can be considered as a general guide.
An oral dosage of up to 200mg/kg/day in divided doses (2 to 4) is recommended for chronic use in some disorders, with lower doses sufficing in other conditions. If clinical and biochemical symptoms do not improve, the dose may be increased on a short-term basis. Higher doses of up to
400mg/kg/day may be necessary in acute metabolic decompensation or the i.v. route may be required.

Haemodialysis - maintenance therapy
If significant clinical benefit has been gained by a first course of intravenous Carnitor then maintenance therapy can be considered using 1g per day of Carnitor orally. On the day of the dialysis oral Carnitor has to be administered at the end of the session.

Method of administration

For oral administration only. The Oral Solution can be drunk directly or diluted further in water or fruit juices.

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

While improving glucose utilisation, the administration of levocarnitine to diabetic patients receiving either insulin or hypoglycaemic oral treatment may result in hypoglycaemia. Plasma glucose levels in these subjects must be monitored regularly in order to adjust the hypoglycaemic treatment immediately, if required.
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 end stage renal disease (ESRD) patients on dialysis may result in an accumulation of the potentially toxic metabolites, trimethylamine (TMA) and
trimethylamine-N-oxide (TMAO), since these metabolites are usually excreted in the urine. This situation has not been observed following intravenous administration of levocarnitine.

There have been very rare reports of International Normalised Ratio (INR) increased in patients treated concomitantly with levocarnitine and coumarinic drugs. See section 4.5 ‘Interactions’ and Section 4.8 ‘Undesirable Effects’.

This medication contains “sodium methyl para-hydroxybenzoate and sodium propyl para-hydroxybenzoate” and may cause allergic reactions (possibly delayed).

This medicine contains less than 1 mmol sodium (23 mg) per 1 ml of oral solution, that is to say essentially “sodium-free”.

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 (see Section 4.4 and 4.8).

4.6 Fertility, pregnancy and lactation

Fertility

In three small clinical studies conducted on fertility, no safety issues were identified, however further studies are required to evaluate the effect of levocarnitine on fertility.

Pregnancy

Reproductive studies were performed 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 a statistically insignificant greater number of post implantation losses at the highest dose tested (600mg/kg daily) as compared with control animals. The significance of these findings in man is unknown. There is no experience of use in pregnant patients with primary systemic carnitine deficiency.

Taking into account the serious consequences in a pregnant woman who has primary systemic carnitine deficiency stopping treatment, the risk to the mother of discontinuing treatment seems greater than the theoretical risk to the foetus if treatment is continued.

Breast-feeding

Levocarnitine is a normal component of human milk. Use of levocarnitine supplementation in nursing mothers has not been studied. Levocarnitine should only be used by nursing mothers if benefit to the mother outweighs any potential risks to the child from excess carnitine exposure.

4.7 Effects on ability to drive and use machines

Levocarnitine paediatric has no influence on the ability to drive and use machines.

4.8 Undesirable effects

Adverse reactions from any source are listed in the table below by MedRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency. Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness. In addition the corresponding frequency category for each adverse drug reaction is based on the following conventions: very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000).

SYSTEM ORGAN CLASS	FREQUENCY	ADVERSE REACTION
Gastrointestinal disorders	Very rare	Vomiting Nausea Diarrhoea Abdominal cramp
General disorders and administration site conditions	Very rare	Body odour

Investigations	Very rare	International Normalised Ratio increased *

* There have been very rare reports of International Normalised Ratio (INR) increased in patients treated concomitantly with levocarnitine and coumarinic drugs (acenocumarol and warfarin) –see Section 4.4 'Special Warnings' and Section 4.5 'Interactions'.

Decreasing the dosage often diminishes or eliminates drug related patient body odour or gastro-intestinal symptoms when present. Tolerance should be monitored very closely during the first week of administration and after any dosage increase.

Reporting of suspected 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. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

There have been no reports of toxicity from levocarnitine overdosage. Overdosage should be treated with supportive care.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Amino acids and derivatives, ATC Code: A16AA01

Levocarnitine is present as a natural constituent in animal tissues, micro-organisms and plants. In man the physiological metabolic requirements are met both by the consumption of food containing carnitine and the endogenous synthesis in the liver and kidneys from lysine with methionine serving as the methyl donor. Only the L-isomer is biologically active, playing an essential role in lipid metabolism as well as in the metabolism of ketone bodies as branched-chain amino acids. Levocarnitine as a factor is necessary in the transport of long-chain fatty acids into the mitochondria - facilitating the oxidation of fatty acids rather than their incorporation into triglycerides. By releasing CoA from its thioesters, through the action of CoA; carnitine acetyl transferase, levocarnitine also enhances the metabolic flux in the Kreb's cycle; with the same mechanism it stimulates the activity of pyruvate dehydrogenase and in skeletal muscle, the oxidation of branched-chain amino acids. Levocarnitine is thus involved, directly or indirectly in several pathways so that its availability should be an important factor controlling not only the oxidative utilisation of fatty acids and ketone bodies but also that of glucose and some amino acids.

5.2 Pharmacokinetic properties

The absorbed levocarnitine is transported to various organ systems via the blood. The presence of membrane-bound proteins in several tissues including red blood cells that bind carnitine, suggest that a transport system in the blood and a cellular system for the collective uptake is present in several tissues. Tissue and serum carnitine concentration depend on several metabolic processes, carnitine bio-synthesis and dietary contributions, transport into and out of tissues, degradation and excretion may all affect tissue carnitine concentrations. It has been demonstrated that pharmacokinetic parameters increase significantly with dosage. Apparent bioavailability in healthy volunteers is about 10-16%. The data suggests a relationship between maximal plasma concentration/dosage, dosage, plasma AUC, dosage/urinary accumulation. Maximum concentration is reached about four hours after ingestion.

5.3 Preclinical safety data

Levocarnitine is a naturally occurring body substance in human beings, plants and animals. Carnitor products are used to bring the level of levocarnitine in the body up to those found naturally. Appropriate pre-clinical studies have been undertaken and show no signs of toxicity at normal therapeutic doses

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Malic acid (E296)
Saccharin sodium (E954)
Sodium methyl hydroxybenzoate (E219)
Sodium propyl hydroxybenzoate (E217)

6.2 Incompatibilities

None known.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

Store below 25°C.
Store in the original carton in order to protect from light.

6.5 Nature and contents of container

10ml amber glass bottles with a fully removable low density polyethylene cap.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Alfasigma S.p.A.,
Via Ragazzi del '99, n.5,
40133 Bologna (BO),
ITALY

8 MARKETING AUTHORISATION NUMBER(S)

PL 48053/0012

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

22/02/2007

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26/11/2020