SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Levocarnitine 1 g Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Levocarnitine 1.0 g

Each 1ml contains 200 mg of levocarnitine

Each 5 ml contains 1 g of levocarnitine

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection

Colourless to yellowish clear solution. Practically free of particles.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Indicated for the treatment of primary and secondary carnitine deficiency in adults, children, infants and neonates.

Secondary carnitine deficiency in haemodialysis patients.

Secondary carnitine deficiency should be suspected in long-term haemodialysis patients who have the following conditions:

1. Severe and persistent muscle cramps and/or hypotensive episodes during dialysis.
2. Lack of energy causing a significant negative effect on the quality of life.
3. Skeletal muscle weakness and/or myopathy.
4. Cardiomyopathy.

5. Anaemia of uraemia unresponsive to or requiring large doses of erythropoietin.
6. Muscle mass loss caused by malnutrition.

4.2 Posology and method of administration

Posology

Adults, children, infants and neonates:

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.

In acute decompensation, dosages of up to 100 mg/kg/day in 3-4 divided doses are recommended. Higher doses have been used although an increase in adverse events, primarily diarrhoea, may occur.

Secondary carnitine deficiency in haemodialysis patients:

It is strongly recommended that, before initiating therapy with Levocarnitine, plasma carnitine is measured. Secondary carnitine deficiency is suggested by a plasma ratio of acyl to free carnitine of greater than 0.4 and/or when free carnitine concentrations are lower than 20 μmol/litre.

A dose of 20mg per kg should be administered as an intravenous bolus at the end of each dialysis session (assuming three sessions per week). The duration of intravenous treatment should be at least three months, which is the time usually required to restore normal muscle levels of free carnitine. The overall response should be assessed by monitoring plasma acyl to free carnitine levels and by evaluating the patient's symptoms. When carnitine supplementation has been stopped there will be a progressive decline in carnitine levels. The need for a repeat course of therapy can be assessed by plasma carnitine assays at regular intervals and by monitoring the patient's symptoms.

Haemodialysis - maintenance therapy

If significant clinical benefit has been gained by a first course of intravenous Levocarnitine then maintenance therapy can be considered using 1g per day of

Levocarnitine orally. On the day of the dialysis oral Levocarnitine has to be administered at the end of the session.

Elderly

No changes in posology are necessary in elderly patients. The observed safety profile in clinical studies is similar in elderly and younger adults (see section 4.4).

Method of administration

For slow intravenous administration over 2-3 minutes.

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’.

INR – or other appropriate tests of coagulation – should be checked weekly until they become stable, and monthly thereafter, in patients taking such anticoagulants together with Levocarnitine.

There have been reports of seizures in patients with previous seizure activity, however it is not clear if Levocarnitine increases the incidence and/or severity of seizure attacks. In instances where levocarnitine is a suspected cause of seizures, consideration should be given to withdrawing treatment with levocarnitine.

High doses and long-term administration of Levocarnitine have been associated with diarrhoea.

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 ‘Special Warnings and Precautions’ and Section 4.8 ‘Undesirable Effects’).

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 into 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 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
Nervous system disorders	Uncommon	Headache
Vascular disorders	Uncommon	Hypertension Hypotension
Gastrointestinal disorders	Common	Vomiting Nausea Diarrhoea Abdominal cramp
	Uncommon	Dysgeusia
Skin and subcutaneous tissue disorders	Uncommon	Skin odour abnormal
	Not known	Pruritus Rash
Musculoskeletal and connective tissue disorders	Uncommon	Muscle spasms
	Not common	Muscle tightness
General disorders and administration site conditions	Uncommon	Feeling abnormal Pyrexia
Investigations	Uncommon	Blood pressure increased
	Very rare	International Normalised Ratio increased*

[#] In patients with previous seizure activity, convulsions have been reported with Levocarnitine treatment (see section 4.4).

* 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

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 branchedchain 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.

Absorption

Levocarnitine is absorbed by the mucosal cells of the small intestine and enters the blood stream relatively slowly; the absorption is probably associated with an active transluminal mechanism.

The apparent systemic availability after oral administration is limited (<10%) and variable.

Distribution

Absorbed levocarnitine is transported to various organ systems via the blood; it is thought that a transport system in the blood and a cellular system for selective uptake is involved.

Excretion

Levocarnitine is excreted mainly in the urine and is variable. The excretion is directly proportional to the blood levels.

Metabolism

Levocarnitine is metabolised to a very limited extent.

5.3 Preclinical safety data

Levocarnitine is a naturally occurring body substance in human beings, plants and animals.

Levocarnitine 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

Hydrochloric acid 10% for pH adjustment

Water for injection

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions. Keep the ampoules in the outer carton in order to protect from light.

6.5 Nature and contents of container

Clear type I glass ampoules, of 5ml capacity.

The ampoules are packed in a white plastic case with capacity to hold 5 ampoules in a carton box.

6.6 Special precautions for disposal

For single use only. Any unused solution should be discarded.

The medicinal product is to be inspected visually for particulate matter and discolouration prior to administration.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

PL 46052/0003

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