EU Risk Management Plan for L-carnitine

RMP Version number: 2

Data lock point for this RMP: 30 January 2016

Date of final sign off: 23 October 2017

Rationale for submitting an updated RMP:

A Risk Management Plan (RMP) for L-carnitine (LC) has been already submitted by the Marketing Authorisation Holder (MAH) in UK on December 2012 for the registration [redacted] LC, registered as a generic. The present version of the RMP is intended to cover all formulations of the product and, therefore, has a wider scope than the previous RMP. This version of the RMP is in line with Module 2.5 of LC dated January 27th, 2017 and related Company Core Safety Information (CCSI) document.

It has been written in accordance with GVP Module V (rev 2) implemented on March 31st, 2017 and the related template.

Details of the currently approved RMP:

RMP of [redacted] LC, registered as a generic

Version number: 1

Approved with procedure: NATIONAL PROCEDURE IN UK

Date of approval (opinion date): 30 July 2013

EU QPPV name: [redacted]

EU QPPV signature: [redacted]

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Part I: Product(s) Overview

Table Part I.1 – Product Overview

Active substance(s) **(INN or common name)**	L-carnitine
Pharmacotherapeutic group(s) (ATC Code)	A16AA01
Marketing Authorisation <Holder> <Applicant>	[redacted]
Medicinal products to which this RMP refers	1 (RMP was submitted [redacted]
Invented name(s) in the European Economic Area (EEA)	[redacted]
Marketing authorisation procedure	National
Brief description of the product	Chemical class: L-carnitine (LC) is a naturally occurring amino acid derivative, produced endogenously in the kidneys and liver. It may be derived from meat and dairy products in the diet. Carnitine is an essential metabolic cofactor for normal fatty acid metabolism but only the L-isomer is biologically active.
	Summary of mode of action: The most important biological function is in the transport of fatty acids into the mitochondria for subsequent β-oxidation, a process that results in the esterification of LC to form acylcarnitine derivatives. As mitochondrial fatty acid oxidation is a fundamental source of cellular energy, particularly in cardiac, hepatic and skeletal muscle, LC is a key component in energy production within human body.
	Important information about its composition: LC is 3-hydroxy-4-N-trimethyl-aminobutyric acid. *Empirical formula:* $C_7H_{15}NO_3$ *Molecular weight:* 161.2 *Chemical name:* (R)-(3-Carboxy-2-hydroxypropyl)trimethylammonium hydroxide, inner salt; (R)-3-Hydroxy-4-trimethylammoniobutyrate
Hyperlink to the Product Information	Not applicable

Indication(s) in the EEA	Current (if applicable): Indications are not the same in all Countries (see the Clinical Overview dated January 27th 2017). The most common one is as follows: Primary and secondary carnitine deficiencies
	Proposed (if applicable): Not applicable
Dosage in the EEA	Current (if applicable): Also for the dosage, some differences may exist from Country to Country (see the Clinical Overview dated January 27th 2017). However, the most common dosages are reported below. ***Oral solution (single dose 1g/10 mL, 2g/10 mL and sol. 30%); tablets 330 mg; chewable tablets:*** *Primary carnitine deficiencies and secondary carnitine deficiency resulting from congenital errors of metabolism:* oral daily dose depends on patient's age and weight: up to 2 years of age: 150 mg/kg bodyweight; from 2 to 6 years of age: 100 mg/kg bodyweight; from 6 to 12 years of age: 75 mg/kg bodyweight; adults and children over 12 years of age: 2-4 g. The dosage required depends upon the severity of presentation at the time of treatment and the medical doctor evaluation. *Secondary carnitine deficiency and haemodialysis:* 2 - 4 g/day. The oral solution (30%) must be drunk after dilution; the oral single dose solution must be diluted in a glass of water. ***Solution for injection – Solution for infusion:*** *Secondary carnitine deficiency and haemodialysis:* 2 g after each dialysis session, slowly intravenously administered. A 2.5 g dosage can be indicated in patients under dialysis for more than 1 year. **5 mL ampoules** Slow intravenous administration over 2-3 minutes. **100 mL and 250 mL infusion bags**

	Infusion administration must be 3 mL/min, i.e. 30 minutes for the 100 mL bags and 1 hour and 20 minutes for the 250 mL bags.
	Proposed (if applicable): Not applicable
Pharmaceutical form(s) and strengths	Current (if applicable): In summary: LC is available worldwide in the following oral formulations: • oral solution 1 g/10 mL • oral solution 2 g/10 mL • chewable tablets 1 g • tablets 330 mg • 1.5 g/5 mL oral solution (oral solution 30%, bottles of 40 mL) • 1.5 g/5 mL oral solution (oral solution 30%, bottles of 20 mL) It is also available as injectable formulations: • solution for injection 1 g/5 mL • solution for injection 2 g/5 mL • 1 bag solution for infusion 1 g/100 mL with sodium chloride • 1 bag solution for infusion 2.5 g/250 mL with sodium chloride • solution for infusion 1 g/100 mL with glucose • solution for infusion 2.5 g/250 mL with glucose
	Proposed (if applicable): Not applicable
Is/will the product be subject to additional monitoring in the EU?	No

Introduction

The International Birth Date (IBD) of L-carnitine (LC) is November 29, 1969. LC was first registered by Sigma-Tau, in Italy, in November 1969 as an oral formulation and in June 1979 as an injectable formulation. Since then, it has been authorized in other 38 Countries around the world. Based on the long presence on the market with recognized efficacy and an acceptable level of safety, LC can be included in the category "well-established medicinal use within the Community". For this reason, according to GVP Module V, a reduced RMP is acceptable.

It has to be noted that a RMP for LC has been already submitted by the Marketing Authorisation Holder (MAH). This submission was done in UK on [redacted] for the registration [redacted] of LC, registered as a generic. Therefore, the submitted version of the RMP was a reduced one (the one applicable to generic products).

It has to be noted, that this version of the RMP is currently used in Pharmacovigilance for signal detection purposes.

This new version of the RMP is intended to cover all formulations of the product and, therefore, has a wider scope than the previous RMP. It is based on GVP Module V, revision 2, issued on March 31st, 2017. This module changed a lot in the last years: it came into effect on July 2012 and since then was revised twice, on April 2014 and March 2017. These changes affected also the RMP template. Consequently, the current new template of the RMP is completely different from what it was in 2012.

For the two reasons illustrated above (wider scope and different format of the new RMP as compared with the previous one), the present document will not track the changes vs the previous version.

However, all significant changes in the content, such as addition/removal of identified and potential risks, as well as all differences in the Safety Plan, will be described and justified.

This new version of the RMP is in line with Module 2.5 dated January 27th, 2017 and related Company Core Safety Information (CCSI) document.

In the continuation, the terms L-carnitine, levocarnitine, LC will all indicate the same drug.

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

SI.1 Epidemiology of the disease

This section includes only the most common indications, i.e. primary and secondary carnitine deficiencies.

Primary systemic carnitine deficiency

Primary systemic carnitine deficiency (Online Mendelian Inheritance in Man [OMIM] 212140) or carnitine uptake defect (CUD) is a fatal autosomal recessive disorder of fatty acid oxidation caused by mutations in the SLC22A5 gene that encodes the sodium ion-dependent carnitine transporter (organic cation/carnitine transporter 2; OCTN2). The OCTN2 transporter is expressed in several human tissues including cardiac and skeletal muscles, small intestine, renal tubules, skin fibroblasts, lymphoblasts, and placenta. The gene, SLC22A5 has been cloned and molecular analysis of its 10 exons has demonstrated diverse mutations. Defects in the OCTN2 carnitine transporter results in autosomal recessive primary carnitine deficiency characterized by decreased intracellular carnitine accumulation, increased losses of carnitine in the urine, and low serum carnitine levels. Patients can present early in life with hypoketotic hypoglycemia and hepatic encephalopathy, or later in life with skeletal and cardiac myopathy or sudden death from cardiac arrhythmia, usually triggered by fasting or catabolic state (Evangeliou and Vlassopoulos, 2003; Sarafoglou *et al*, 2010; Tamai, 2013). Deficiency of the OCTN2 carnitine transporter is the only cause of primary carnitine deficiency.

Primary carnitine deficiency has a frequency of about 1:40,000 new-borns in Japan, and 1:37,000 to 1:100,000 in Australia, with frequencies in Europe and the US that seems to be similar to that reported in Japan (Longo *et al*, 2006; Reuter and Evans, 2012). The highest prevalence reported in the world (1:300) is in the Faroe Islands, where primary carnitine deficiency subjects are predominantly asymptomatic (Rasmussen *et al*, 2014).

Expanded new-born screening (NBS) for free carnitine levels has enabled the identification of heterozygous infants of undiagnosed mothers affected with primary carnitine deficiency, which in turn leads to the identification of other undiagnosed heterozygous family members. Heterozygous individuals of a single OCTN2 transporter mutation (OCTN2 carriers) receive far less attention than homozygous or compound heterozygous individuals (have different paternal and maternal mutation of the gene) for primary carnitine deficiency. However, there is an increasing recognition that heterozygotes for mutations of genes involved in fatty acid oxidation may become symptomatic under environmental stress (fasting, prolonged exercise and illness) (Reuter and Evans, 2012).

Affected patients can have a predominant metabolic or cardiac presentation. The metabolic presentation is more frequent before 2 years of age, consisting in upper respiratory tract infection or acute gastroenteritis, followed by lethargy and minimal responsiveness to stimuli. Hepatomegaly is frequent in these patients, while laboratory tests usually show hypoketotic hypoglycaemia and hyperammonaemia. Cardiomyopathy is more frequent in older patients sometimes associated to hypotonia, with enlarged heart and decreased ventricular ejection fraction (EF) (Longo *et al*, 2006).

Defects in the OCTN2 carnitine transporter responds to pharmacological doses of L-carnitine, which can enter cells using other transporters such as the organic cation/carnitine transporter 1 (OCTN1) a low-affinity sodium-independent carnitine transporter (Tamai *et al*, 1998), and the amino acid transporter B(0,+) (Ganapathy and Ganapathy, 2005; Longo *et al*, 2006).

Mortality and morbidity (natural history)

Systemic carnitine deficiency is often fatal, the age of death ranging in the interval 7-28 years (Dollery, 1999). Primary carnitine deficiency is associated with a sudden death in newborns (Scaglia, 2017). There may also be progressive cardiomyopathy at a later age (Longo *et al*, 2006). Hypoglycemic hypoketotic encephalopathy is a condition noted in younger infants with primary carnitine deficiency (Scaglia, 2017).

Demographics of the target population – age, sex, race/ethnic origin

Primary systemic carnitine deficiency may occur from infancy to adolescence. The mean age at onset for primary carnitine deficiency not detected or ascertained by a newborn screening program is 2 years, with onset ranging from 1 month to 7 years (Pons and De Vivo, 1995; Scaglia, 2017). Infants typically present with hypoketotic hypoglycemia, whereas older children present with skeletal or heart myopathy. Symptoms of muscle carnitine deficiency may appear early yet generally occur later (i.e., second or third decade of life). The condition is panethnic and has no gender predilection (Scaglia, 2017). Affected patients can have a predominant metabolic or cardiac presentation. The metabolic presentation is more frequent before two years of age (Longo *et al*, 2006); Cardiomyopathy is more frequent in older patients associated sometimes with hypotonia (Longo *et al*, 2006) Several patients with primary carnitine deficiency have been identified by newborn screening programs in the past few years (Longo *et al*, 2006).

Secondary carnitine deficiency

Secondary carnitine deficiency is associated with several inborn errors of metabolism and acquired medical or iatrogenic conditions (Evangeliou and Vlassopoulos, 2003).

The role of the carnitine system in cell metabolism is mainly known in mitochondria where the interaction between fatty acid and glucose metabolism is fundamental for cell energy production (Bremer, 1997). The crucial role of LC in the transfer of long-chain fatty acids across the inner mitochondrial membrane requires, besides the OCTN2 transporter, enzymes that conjugate it with long chain fatty acids (carnitine palmitoyl transferase 1, CPT1), transfer the acylcarnitine across the inner plasma membrane (carnitine-acylcarnitine translocase, CACT), and conjugate the fatty acid back to CoA for subsequent beta oxidation (carnitine palmitoyl transferase 2, CPT2) (Longo *et al*, 2006). Carnitine acetyltransferase (CRAT) enzyme located on the matrix side of the inner mitochondrial membrane, is important for the synthesis of short-chain acylcarnitine and for the production of free CoA (Ramsay and Naismith, 2003; Violante *et al*, 2013).

Inborn causes of secondary carnitine deficiency include a number of inherited metabolic errors. Among the others, the enzymes involved in LC function: CPT1, CACT, CPT2 and CRAT (Pons and De Vivo, 1995).

Defects in the liver isoform of CPT1 (CPT1-A) present with recurrent attacks of fasting hypoketotic hypoglycaemia, usually between birth and 18 months of age, with altered mental status and hepatomegaly. The heart and the muscle, which express a genetically distinct form of CPT1 (CPT1-B), are usually unaffected; these patients usually have elevated levels of plasma carnitine (Longo *et al*, 2006). CPT1-B

defects have not been hitherto identified, although a plausible genetic variant regulating CPT1-B expression has been associated with narcolepsy (Miyagawa *et al*, 2008).

The first disease caused by the brain isoform CPT1-C was recently described in humans, with CPT1-C being identified as the gene causing hereditary spastic paraplegia (Rinaldi *et al*, 2015).

CACT deficiency presents in most cases in the neonatal period with hypoglycaemia, hyperammonaemia, and cardiomyopathy with arrhythmia leading to cardiac arrest. Seizures and apnoea may also occur. Plasma carnitine levels are usually extremely reduced, with a marked increase in long-chain acylcarnitines. The episodes repeat over time with progressive neurological, cardiac, and hepatic deterioration (Longo *et al*, 2006).

CPT2 deficiency has several clinical presentations. Deficiency of CPT2 presents more frequently in adolescents or young adults with rhabdomyolysis triggered by prolonged exercise, but can also present in infancy and in the neonatal period. More severe variants of CPT2 deficiency present in the neonatal period similarly to CACT deficiency associated or not with multiple congenital anomalies (respiratory distress, seizures, altered mental status, hepatomegaly, cardiomegaly, cardiac arrhythmia, dysmorphic features, renal dysgenesis, and neuronal migration defects). The neonatal form is rapidly fatal and responds poorly to therapy (Longo *et al*, 2006).

CRAT deficiency is very rare and present with disturbancies in brain, heart, and kidney functions in association with poor respiration and failure to thrive (Di Donato *et al*, 1979; Przyrembel, 1987).

Among the heterogeneous group of secondary carnitine deficiencies, the organic acidaemias (in some papers reported as acidurias) are of particular interest, because they suggest a new physiological role for carnitine in intermediary metabolism. Carnitine deficiency has been recognized in long- and medium-chain acyl-CoA dehydrogenase deficiency, isovaleric acidaemia (IVA), glutaric aciduria, propionic acidaemia (PA), methyl-malonic acidaemia (MMA), and short-chain acyl-CoA dehydrogenase deficiency (Rebouche and Paulson, 1986).

Classical MMA is a relatively rare inborn error of branched-chain amino acid metabolism, occurring in 1:50,000 to 1:80,000 new-born (Hörster and Hoffmann, 2004). PA is an autosomal recessive disorder caused by deficiency of propionyl CoA, the enzyme that converts propionyl CoA to methyl-malonyl CoA with the help of the cofactor biotin. As a result of defective propionyl CoA carboxylase, propionyl CoA accumulates and combines with oxaloacetate, another intermediate of the citric cycle, to form methylcitric acid, the diagnostic metabolite of propionic acidaemia. Most cases of propionic acidaemia present with lethargy progressing to coma from 16 h to weeks after birth, depending on the severity of the enzyme impairment caused by the genetic lesion. Patients can have severe hyperammonaemia associated or not with metabolic acidosis. Hyperammonaemia is an important contributor to brain damage or death in these children (Filipowicz *et al*, 2006). IVA is a disorder of leucine catabolism caused by deficient activity of isovaleryl-CoA dehydrogenase with autosomal recessive inheritance (Roe *et al*, 1990; Mayatepek *et al*, 1991; de Sousa *et al*, 1986; Itoh *et al*, 1996).

Chalmers *et al* (1984) have shown that total carnitine excretion in most patients with various organic acidaemias was higher than the range of controls, suggesting that carnitine is utilized as a means of removing excess organic acids. In these disorders, carnitine may act as an intra-mitochondrial buffer to remove excess acyl moieties, allowing regeneration of free CoA to be used to maintain normal metabolic functions of the mitochondrion (Rebouche and Paulson, 1986).

Acquired medical conditions which may cause carnitine deficiency include chronic renal disease, malabsorption (cystic fibrosis, short-gut syndrome), extreme prematurity, and carnitine-deficient diet (Shannon and Wolfe, 1997).

In cirrhosis and chronic renal failure, carnitine biosynthesis is impaired or carnitine is lost during haemodialysis. Other chronic conditions like diabetes mellitus, heart failure, and Alzheimer disease may cause carnitine deficiency also observed in conditions with increased catabolism as in critical illness. Preterm neonates develop carnitine deficiency due to impaired proximal renal tubule carnitine re-absorption and immature carnitine biosynthesis (Evangeliou and Vlassopoulos, 2003). Moreover, total parenteral nutrition (TPN) lacks carnitine and exposes very low birth weight infants to carnitine deficiency, with decreased production of ketones from long-chain fatty acids (Scaglia and Longo, 1999).

Examples of iatrogenic factors determining carnitine deficiency are chronic administration of valproic acid (VPA), pivalic acid, chemotherapy, and chronic haemodialysis (Shannon and Wolfe, 1997).

Carnitine deficiency can mimic other disorders and secondary carnitine deficiency is, by definition, found in conjunction with other abnormalities. There are, however, a series of signs and symptoms that can alert to the possibility of carnitine deficiency, including failure to thrive, recurrent infections, hypotonicity, lethargy, cardiomyopathy, and liver dysfunction (Shannon and Wolfe, 1997).

Mortality and morbidity (natural history)

Not known as patients are typically suffering from other conditions and comorbidities.

Demographics of the target population – age, sex, race/ethnic origin

No significant prevalence of these disorders is found between genders or in different ethnic groups (Dollery, 1999). In secondary carnitine deficiency caused by fatty acid oxidation disorders, the age of onset varies. Genetically determined metabolic errors may produce symptoms in children aged 0-13 years. Metabolic decompensation triggered by viral illness, associated with encephalopathy, and accompanied by liver involvement, hypotonia, or cardiomyopathy tends to occur in infancy. Cardiomyopathy or skeletal myopathy tends to present later. Carnitine deficiency also may occur in preterm newborns receiving total parenteral nutrition (TPN) with no carnitine supplementation (Scaglia, 2017).

SI.2 Concomitant medication(s) in the target population

Dextrose: Hypoglycemic episodes associated with carnitine deficiency are treated with intravenous dextrose infusion or proper feeding and diet. Maintaining normal carnitine levels through supplementation and preventing hypoglycemia through frequent feeding and diet can prevent the metabolic, hepatic, cardiac, and muscular complications of systemic primary carnitine deficiency (CDSP) (El-Hattab, 2012).

Metronidazole: Oral metronidazole and/or decreasing the carnitine dose usually results in the resolution of the fishy odor due to LC supplementation and trimethylamine production (El-Hattab, 2012). A course of oral metronidazole at a dose of 10 mg/kg/day for 7–10 days may be indicated (Thompson *et al*, 1990; Miller *et al*, 2016).

Diet and supplements: the primary metabolic defect can be treated with specific diet and other supplements, such as riboflavin, glycine, or biotin (MedScape). Some patients require supplementation with medium-chain triglycerides and essential fatty acids (eg, linoleic acid, linolenic acid). Patients with a fatty acid oxidation disorder require a high-carbohydrate, low-fat diet (MSD Manual).

SI.3 Important co-morbidities found in the target population

By its very definition, secondary carnitine deficiency is always associated with another condition or comorbidity. In general, secondary carnitine deficiency is associated with several inborn errors of metabolism and acquired medical or iatrogenic conditions (Evangeliou and Vlassopoulos, 2003). The comorbidities of this target population are therefore complex and wide-ranging.

Inborn errors of metabolism

These are metabolic disorders due to genetic causes and can be split into two main categories: organic acidurias and fatty acid oxidation defects.

Fatty acid oxidation defects – these are the most frequent causes of secondary carnitine deficiency and include a number of inherited metabolic errors involving the other enzymes involved in LC function, such as CPT1 (carnitine palmitoyl transferase 1); CPT2 (carnitine palmitoyl transferase 2) and CACT (carnitine-acylcarnitine translocase); which determine carnitine deficiency (Pons and De Vivo, 1995). Defects in the liver isoform of CPT1 present with symptoms usually between birth and 18 months of age (Longo *et al*, 2006). CACT deficiency presents in most cases in the neonatal period. Deficiency of CPT2 present more frequently in adolescents or young adults with rhabdomyolysis triggered by prolonged exercise, but can also present in infancy and in the neonatal period. More severe variants of CPT2 deficiency present in the neonatal period similarly to CACT deficiency associated or not with multiple congenital abnormalities (respiratory distress, seizures, altered mental status, hepatomegaly, cardiomegaly, cardiac arrhythmia, dysmorphic features, renal dysgenesis, and neuronal migration defects). The neonatal form is rapidly fatal and responds poorly to therapy (Longo *et al*, 2006).

Organic acidurias – the principal amino acid oxidation disorders leading to secondary carnitine deficiencies include: long- and medium-chain acyl-CoA dehydrogenase deficiency; isovaleric acidemia; glutaric aciduria; propionic and methylmalonic acidemia; short-chain acyl-CoA dehydrogenase deficiency (Rebouche and Paulson, 1986). These diseases present during infancy, with an asymptomatic period observed from birth until the appearance of the first symptoms (Scaglia, 2017).

Acquired Medical Conditions

Acquired medical conditions which may cause carnitine deficiency include chronic renal disease, malabsorption (cystic fibrosis, short-gut syndrome), extreme prematurity, and carnitine-deficient diet (Shannon and Wolfe, 1997). Other chronic conditions like diabetes mellitus, heart failure, and Alzheimer disease may cause carnitine deficiency also observed in conditions with increased catabolism as in critical

illness. Preterm neonates develop carnitine deficiency due to impaired proximal renal tubule carnitine re-absorption and immature carnitine biosynthesis (Evangeliou and Vlassopoulos, 2003). Total Parenteral Nutrition (TPN) solutions lack LC content and so expose very low birth weight infants to carnitine deficiency (Scaglia and Longo, 1999). Young children and premature babies have immature enzymatic systems which cannot synthesis sufficient levels of endogenous carnitine and may develop serious carnitine deficiency when treated with TPN (Scaglia, 2017).

Part II: Module SII - Non-clinical part of the safety specification

According to GVP Module V, this module can be omitted since LC can be categorized as a "well-established use" medicinal product.

Part II: Module SIII - Clinical trial exposure

According to GVP Module V, this module can be omitted since LC can be categorized as a "well-established use" medicinal product.

Part II: Module SIV - Populations not studied in clinical trials

According to GVP Module V, this module can be omitted since LC can be categorized as a "well-established use" medicinal product.

Part II: Module SV - Post-authorisation experience

According to GVP Module V, this module can be omitted since LC can be categorized as a "well-established use" medicinal product.

Part II: Module SVI - Additional EU requirements for the safety specification

According to GVP Module V, this module can be omitted since LC can be categorized as a "well-established use" medicinal product.

Part II: Module SVII - Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

Risk Class	Risk Description
Important identified risks	Accumulation of potentially toxic metabolites in patients with renal insufficiency
	Use in patients with fructose intolerance, glucose-galactose malabsorption and sucrase-isomaltase insufficiency
	Reproductive and congenital toxicities in pregnant/lactating females
	Mild GI complaints and body odour
	Interaction with insulin or oral hypoglycaemic treatment in patients with diabetes
	Hypersensitivity to levocarnitine or any of its excipients
	Off-label use
	Overdose
	Medication errors
Important potential risks	Seizures
	Coumarinic drug interactions
Important missing information	Elderly

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

The following risks were present in the previous version of the RMP (submitted in UK) and categorized in the same way; however, in the updated version of the RMP they have been formulated more accurately:

Hypersensitivity to levocarnitine (LC) or any of its excipients (in particular sucrose and sorbitol, which are contained within some oral formulations of LC (1.5 g/5 mL, bottles of 20 or 40 mL and Chewable tablets 1 g). The previous version of the RMP was only focused on sucrose and sorbitol.

Increased incidence and/or severity of seizure attacks in patients with previous seizure activity or underlying predisposing conditions. The previous version of the RMP only mentioned Seizure.

Reproductive and congenital toxicity, which was reported as a potential risk in the previous version of the RMP, has been now reported as missing information. In fact, no clinical study has been conducted in pregnant women with primary or secondary carnitine deficiencies.

"Mild gastrointestinal complaints and body odor", which were reported as a potential risk in the previous version of the RMP, has been dropped in the updated version of the RMP because this is not considered an important potential risk.

Finally, the potentials for off-label use, medication errors and overdose have been removed based on the evidence of the collected data.

All above described changes are new proposals from the MAH. The scientific evidence that has led to the reclassification/removal above described is provided in section SVII.3.

All changes are described in a tabular format in Annex 8 of the present RMP.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

Important Identified Risks:

Identified Risk: Hypersensitivity to levocarnitine or any of its excipients (in particular sucrose and sorbitol, which are contained within some oral formulations of levocarnitine (1.5 g/5 mL, bottles of 20 or 40 mL and Chewable tablets 1g) and para-hydroxy-benzoates (methyl para-hydroxy-benzoates and propyl para-hydroxy-benzoates), which are contained in the oral formulation (1 g/10 mL and 1.5 g/5 mL))	
Potential mechanisms	How primary sensitization occurs and how the immune system is initially involved is unclear, but once a drug stimulates an immune response, cross-reactions with other drugs within and between drug classes can occur. Fructose intolerance, glucose-galactose malabsorption and sucrase-isomaltase insufficiency render an individual not able to digest nutritionally important carbohydrates, including sucrose and sorbitol, which are contained in some oral formulations of LC.
Evidence source(s) and strength of evidence	Module 2.5 dated January 27th, 2017. Limsuwan and Demoly, 2010; Demoly *et al*, 2007; Bernard Y-H Thong and Teck-Choon Tan, 2011. *MSD Manual:* http://www.msdmanuals.com/professional/immunology-allergic-disorders/allergic,-autoimmune,-and-other-hypersensitivity-disorders/drug-hypersensitivity http://ghr.nlm.nih.gov http://emedicine.medscape.com: Guandalini, 2017.
Characterization of the risk (frequency, severity, reversibility, outcomes, impact on quality of life)	Based on the available data (Module 2.5 dated January 27th, 2017), local or mild to moderate systemic hypersensitivity reactions, such as "Rash" or "Pruritus", can be expected after levocarnitine administration; the actual frequency is not known. Nine events of such reactions were reported in a total of 1636 patients treated in sponsored studies and studies from literature. The reported ADRs were "Rash" (2), "Pruritus" (2) and, for the iv formulation, "Injection site reactions" (5). In addition, 25 events of "Rash" and 22 of "Pruritus" were collected in post-marketing.

Identified Risk: Hypersensitivity to levocarnitine or any of its excipients (in particular sucrose and sorbitol, which are contained within some oral formulations of levocarnitine (1.5 g/5 mL, bottles of 20 or 40 mL and Chewable tablets 1g) and para-hydroxy-benzoates (methyl para-hydroxy-benzoates and propyl para-hydroxy-benzoates), which are contained in the oral formulation (1 g/10 mL and 1.5 g/5 mL))	
	Few systemic reactions with cardiovascular and/or respiratory involvement, all classifiable as mild to moderate systemic reactions, were observed in post-marketing. The MAH considers the risk of "Anaphylactic Reaction" extremely remote if not null. In fact, according to the definition of Anaphylactic Reaction reported in the Merck Manual and other current international Guidelines, only one such case was reported in post-marketing. The outcome of the local or mild to moderate systemic hypersensitivity reactions is generally benign. Patients with fructose intolerance, glucose-galactose malabsorption and sucrase-isomaltase insufficiency have incapacity to digest nutritionally important carbohydrates including sucrose and sorbitol, which are contained within some oral formulations of levocarnitine (1.5 g/5 mL, bottles of 20 or 40 mL and Chewable tablets 1 g). Therefore, ingestion of these oral levocarnitine formulations may result in the production of symptoms as described below. Carbohydrate malabsorption generally carries a low mortality risk although morbidity can be severe depending on the specific syndrome. Morbidity is implicit for untreated patients with fructose intolerance who can develop hypoglycaemia and acidosis which may act together to produce organ shock or coma. The symptoms are often dramatic and difficult to miss. Neonates and infants with glucose-galactose malabsorption are at particular risk of chronic diarrhoea and malnutrition, with stomach cramps, bloating, excess gas production and diarrhoea being common symptoms of sucrase-isomaltase insufficiency.
Background incidence/prevalence	Hypersensitivity incidence/prevalence to Levocarnitine cannot be estimated from the available data. Hereditary fructose intolerance is considered rare, with less than 1 in 10,000 individuals affected. Glucose-galactase malabsorption and sucrase-isomaltase insufficiency are also rare (1 in 5,000 people of European descent are affected by the latter; a few hundred cases being reported for the former), with a more common incidence seen in Greenland, Alaska and Canadian Eskimos.
Risk factors and risk groups	Patients with history of levocarnitine hypersensitivity. Patients with fructose intolerance, glucose-galactose malabsorption, or sucrase-isomaltase insufficiency.

Identified Risk: Hypersensitivity to levocarnitine or any of its excipients (in particular sucrose and sorbitol, which are contained within some oral formulations of levocarnitine (1.5 g/5 mL, bottles of 20 or 40 mL and Chewable tablets 1g) and para-hydroxy-benzoates (methyl para-hydroxy-benzoates and propyl para-hydroxy-benzoates), which are contained in the oral formulation (1 g/10 mL and 1.5 g/5 mL))	
Preventability	The identified risk factors (i.e. *history of levocarnitine hypersensitivity, presence of* fructose intolerance, glucose-galactose malabsorption, or sucrase-isomaltase insufficiency) has been reported in the Product Information documents.
Impact on the risk-benefit balance of the product	No significant impact in the benefit/risk profile of the product as only local or mild to moderate hypersensitivity systemic reactions were observed.
Public health impact	The impact on public health is considered minimal due to the fact that the observed hypersensitivity reactions are local or mild to moderate in severity.

Identified Risk: Accumulation of potentially toxic metabolites trimethylamine (TMA) and trimethylamine-N-oxide (TMAO) in patients with severe renal impairment (oral formulations)	
Potential mechanisms	Trimethylamine (TMA) and trimethylamine-N-oxide (TMAO) are short-chain aliphatic amines derived from intestinal bacterial metabolism of the dietary products. Both of these substances are normally removed by urinary excretion; so, accumulation of these substances may be observed in ESRD patients with abnormal renal function. In addition, patients with ESRD have qualitatively different and a greater number of bacterial populations in the small intestine compared with people with normal renal function. This results in an increase in the generation of short-chain aliphatic methylamines from dietary precursors in ESRD patients. Carnitine and its metabolites TMA and TMAO, produced by intestinal bacterial degradation (Eknoyan *et al*, 2003; Schreiber, 2002), are eliminated from the body mainly via urinary excretion (Evans, 2003). It follows that chronic administration of oral levocarnitine to patients with severely compromised renal function, or in ESRD and on dialysis may result in accumulation of potentially toxic metabolites: TMA and TMAO.
Evidence source(s) and strength of evidence	Module 2.5 dated January 27th, 2017. http://emedicine.medscape.com: Gulati, 2015. Bain *et al*, 2006b; Hsu *et al*, 2004; Evans, 2003; Eknoyan *et al*, 2003; Schreiber, 2002.
Characterization of the risk (frequency, severity, reversibility, outcomes, impact on quality of life)	The potential toxic effects of these metabolites have not been elucidated. <u>Pre-clinical studies</u> This risk was first identified as potential during nonclinical PK studies. Following oral administration of labelled LC in rats, two metabolites were identified in the urine and faeces, namely TMA

Identified Risk: Accumulation of potentially toxic metabolites trimethylamine (TMA) and trimethylamine-N-oxide (TMAO) in patients with severe renal impairment (oral formulations)	
	(primarily in urine) a precursor of TMAO and gammabutyrobetaine (primarily in faeces), accounting for up to 23% and 31% of the administered dose, respectively. Published clinical data The extent of the accumulation of these metabolites has been investigated in six patients with ESRD undergoing haemodialysis following oral administration of LC 1 g daily for 12 days (Bain *et al*, 2006b). Although plasma levels of TMA remained unaltered, pre-dialysis plasma concentrations of TMAO increased significantly and continued to rise during the study. Observed adverse events According to the most updated integrated summary of safety data (Module 2.5 dated January 27th, 2017), ten events in the nervous system disorders SOC were reported in a total of 1636 patients treated in sponsored studies and studies from literature. The reported ADRs were "Dizziness" (1), "Headache" (4), "Paraesthesia" (2), "Convulsion" (2), "Cerebrovascular disorder" (1). These events were also reported in post-marketing: "Dizziness" (11), "Headache" (17), "Paraesthesia" (7), and "Convulsion" (29). The clinical significance of TMA is related to its potential to contribute to neurological toxicity in ESRD patients. Bain says that TMA and TMAO have the potential to form the carcinogen nitrosodiumdimethylamine and so makes the hypothesis that accumulation of these substances may contribute to an increase in cancer in ESRD patients (Bain *et al*, 2006b).
Background incidence/prevalence	Global prevalence of chronic kidney disease (CKD) – a precursor to ESRD – in children is approximately 18.5-58.3 per million children and is much lower than in adults. There is also a difference with respect to ethnicity, with blacks having a 2.7 times higher rate of ESRD than white individuals (Gulati, 2015). The incidence of ESRD is increasing with a figure of 650,000 new cases projected for 2010 (Hsu *et al*, 2004). The increased incidence may be due to the increasing use of nephrotoxic agents such as analgesic medicines and the greater success rate of delivering low birth weight babies, since CKD is more common with increased prematurity (Hsu *et al*, 2004; Gulati, 2015).
Risk factors and risk groups	Patients with severely compromised renal function or ESRD patients on dialysis, who require chronic administration of high doses of LC.
Preventability	The identified risk factors (i.e. patients with severe renal insufficiency and ESRD) must be reported in the Product Information documents.

Identified Risk: Accumulation of potentially toxic metabolites trimethylamine (TMA) and trimethylamine-N-oxide (TMAO) in patients with severe renal impairment (oral formulations)	
Impact on the risk-benefit balance of the product	The impact in the benefit/risk profile of the product is considered moderate due to the fact that ESRD patients are part of the target population.
Public health impact	The impact on public health is considered manageable through the product information documents.

Important Potential Risks:

Potential Risk: Increased incidence and/or severity of seizure attacks in patients with previous seizure activity or underlying predisposing conditions	
Potential mechanisms	Seizure may have a higher incidence in the target population of LC (patients with primary and secondary carnitine deficiency) than in the general population because of a variety of etiologic factors including underlying metabolic diseases, nutritional inadequacy, concomitant treatments such as anticonvulsant (Coulter, 1995). For example, Valproic acid is an anticonvulsant medicine taken for the treatment of seizures. Since several studies have shown that plasma carnitine levels are significantly lower in patients taking valproate than in controls, some physicians treat these patients with LC to restore plasma levels.
Evidence source(s) and strength of evidence	Module 2.5 dated January 27th, 2017. Epilepsy Health Center: http://www.webmd.com/epilepsy/guide/epilepsy-causes http://emedicine.medscape.com: Ko, 2016. Coulter, 1995.
Characterization of the risk (frequency, severity, reversibility, outcomes, impact on quality of life)	Several cases of convulsions were reported in post-marketing, while only two cases of convulsion/epilepsy have been detected during the conduction of two sponsored clinical trials, one of which in a patient with a cerebral lesion (calcified lesion in the right frontal lobe and calcified right fronto-parietal arterio-venous malformation) that was considered as the most likely cause of the seizure activity. Seizures have been reported to occur in patients with or without pre-existing seizure activity, receiving either oral or intravenous LC. However, the vast majority of the reported seizure cases regarded patients with previous seizure activity or with underlying predisposing conditions. Therefore, in the current version of the CCSI, the risk concerning seizure has been formulated as follows: "In patients with previous seizure activity, LC treatment can increase the incidence and/or severity of the seizure attacks. In patients with underling predisposing conditions, LC treatment could trigger the convulsive crisis". The impact of an increased incidence or severity of seizure on the quality of life of the patients may be significant because of the

Potential Risk: Increased incidence and/or severity of seizure attacks in patients with previous seizure activity or underlying predisposing conditions	
	possible consequences of the convulsive crises: burns, trauma, injuries, such as ecchymosis, haematomas, abrasions, tongue, facial, and limb lacerations.
Background incidence/prevalence	Seizures are a common, nonspecific manifestation of neurologic injury and disease. The lifetime likelihood of experiencing at least 1 epileptic seizure is about 9%, and the lifetime likelihood of receiving a diagnosis of epilepsy is almost 3%. However, the prevalence of active epilepsy is only about 0.8%, with an estimated 180,000 new cases reported per year, of which, approximately 30% of these cases affect children in the US, with studies in several other countries indicating similar numbers (Ko, 2016). Regarding morbidity, trauma is not uncommon among people with generalised tonic-clonic seizures. Injuries such as ecchymosis; haematomas; abrasions; and tongue, facial, and limb lacerations often develop as a result of the repeated tonic-clonic movements. Atonic seizures are also frequently associated with facial and neck injuries. Worldwide, burns are the most common serious injury associated with epileptic seizures. Regarding mortality, seizures cause death in a small proportion of individuals. Most deaths are accidental due to impaired consciousness. However, sudden unexpected death in epilepsy (SUDEP) is a risk of having epilepsy, and it may occur even when patients are resting in a protected environment (i.e. in a bed with rail guards or in the hospital). The incidence of SUDEP is low, about 2.3 times higher than the incidence of sudden death in the general population (Ko, 2016).
Risk factors and risk groups	Patients taking levocarnitine who have a pre-existing history of seizures or having underlying predisposing conditions.
Preventability	The identified risk factors (i.e. patients with pre-existing history of seizures or having underlying predisposing conditions) must be reported in the Product Information documents.
Impact on the risk-benefit balance of the product	The impact on the risk-benefit balance for the product is considered minimal because, only in a few number of patients with previous seizure activity, LC treatment increased the incidence and/or severity of the seizure attacks. In particular in patients with underling predisposing conditions LC treatment could trigger the convulsive crisis.
Public health impact	Public health impact cannot be evaluated in this phase. However, an appropriate sentence has been added in the product information documents (section Warning of SmPC and PIL).

Potential Risk: Hypoglycaemia in diabetic patients receiving either insulin or hypoglycaemic oral treatment (interaction)	
Potential mechanisms	LC improves glucose utilization. Diabetes is a condition in which blood glucose levels are not controlled by endogenous insulin and are therefore high if untreated. Type I diabetic patients take exogenous insulin to stimulate glucose uptake from the blood. Given that LC may improve utilization of glucose, this can result in an overcompensation of glucose levels causing hypoglycaemia. Similarly, Type II diabetics may take oral treatment to reduce blood glucose levels, and the additional action of LC, may result in blood glucose levels being over reduced resulting in hypoglycaemia.
Evidence source(s) and strength of evidence	Module 2.5 dated January 27th, 2017. Dollery, 1999; Kletzmayr *et al*, 1999; Turchin *et al*, 2009.
Characterization of the risk (frequency, severity, reversibility, outcomes, impact on quality of life)	Improving the utilisation of glucose, LC may induce hypoglycaemic state in presence of exogenous insulin or use of hypoglycaemic drugs. No data regarding this risk were collected during the clinical development. This risk is based on a cluster of seven cases of hypoglycemia, none serious, reported to Sigma-Tau in the course of 1991 and all occurred in diabetic patients and a fatal case of hypoglycemia reported in April 2002, occurred to a 91-year-old patient in very poor physical condition. In addition, in a study reported by Kletzmayr *et al* in 1999, one diabetic patient withdrew consent after two weeks of levocarnitine supplementation, as he observed an increase in blood glucose and insulin requirement. Dollery in 1999 reported occasional transient hypoglycaemia in non-insulin dependent diabetes mellitus patients treated with oral hypoglycaemic agents and concomitant LC and one case of an 8 year old child with ethylmalonic-adipic aciduria responsive to riboflavin, who was administered oral levocarnitine and had recurrent and spontaneous hypoglycaemia. Iatrogenic hypoglycemia may cause recurrent morbidity in patients with type 1 and type 2 diabetes.
Background incidence/prevalence	Hypoglycemia was observed in 7.7% of diabetic patients admissions Turchin *et al*, 2009.
Risk factors and risk groups	Patients treated for diabetic disease.
Preventability	Awareness of the risk of interaction through the Product Information documents. Most people feel symptoms of hypoglycemia when their blood sugar is 70 milligrams per deciliter (mg/dL) or lower. Early symptoms include: Confusion, Dizziness, Feeling shaky, Hunger, Headaches, Irritability, Pounding heart; Racing pulse, Pale skin, Sweating, Trembling, Weakness and Anxiety.

Potential Risk: Hypoglycaemia in diabetic patients receiving either insulin or hypoglycaemic oral treatment (interaction)	
Impact on the risk-benefit balance of the product	No significant impact on the benefit/risk profile of the product, because, in diabetic patients, LC improves insulin sensitivity by determining an increase of whole body glucose uptake. Only a regular monitoring of plasma glucose levels is advised in these patients.
Public health impact	The public health impact is considered negligible. However, an appropriate sentence has been added in the product information documents (section Warning of SmPC and PIL).

Potential Risk: Increased anticoagulant effect of Coumarinic drug (interaction)	
Potential mechanisms	Coumarinic drugs inhibit the vitamin K-dependent synthesis of the biologically active forms of calcium-dependent clotting factors II, VII, IX and X. When this occurs, these coagulation factors are no longer capable of binding to the endothelial surface of blood vessels, and are thus biologically inactive. The result of coumarinic use, therefore, is to diminish blood clotting in the patients. The safety and efficacy of the coumarinic therapy is dependent on the maintenance of the INR within the target range for the considered indication. There are some reports that LC may potentiate the hypoprothrombinemic effects of warfarin and other oral anticoagulants from coumarin class. The mechanism of interaction is still unknown. There have been some isolated case reports of INR increase and/or hemorrhage in patients treated with warfarin following the addition of LC therapy. After discontinuation of LC, INR levels returned to normal (Bachmann and Hoffmann, 2004).
Evidence source(s) and strength of evidence	Module 2.5 dated January 27th, 2017. Internal Signal Detection Report "Evaluation of the Effect of L-carnitine and Coumarinic Drugs on INR", version 1.0 dated 19 March 2012. Martinez *et al*, 1993; Bachmann and Hoffmann, 2004.
Characterization of the risk (frequency, severity, reversibility, outcomes, impact on quality of life)	LC might increase the effect of coumarinic drugs and might slow blood clotting too much. The final result can be an increased risk of uncontrolled bleeding. No data regarding this potential risk were collected during clinical development. There have been very rare reports of INR increase in patients treated concomitantly with LC and cumarinic drugs. In order to put the risk of this drug-drug interaction into perspective, the frequency and the clinical relevance (intensity) of the increase of INR, as well as its association to a hemorrhagic risk, have been analysed by the MAH. After evaluating the above

Potential Risk: Increased anticoagulant effect of Coumarinic drug (interaction)	
	findings, the effect of the interaction between LC and coumarinic drugs on the increase of the INR could not be excluded, although no interaction was observed in rats between LC and warfarin on prothrombin time, and no significant biological plausibility was ascertained from the examined literature.
Background incidence/prevalence	The incidence was 0.001%, which was classified as "Very Rare" (i.e. less than 1/ 10,000 cases).
Risk factors and risk groups	Patients receiving anticoagulant treatment with coumarinic drugs.
Preventability	Awareness of the risk of interaction through the Product Information documents.
Impact on the risk-benefit balance of the product	No significant impact in the benefit/risk profile of the product because since this effect is preventable and manageable.
Public health impact	Public health impact is expected to be negligible because there have been very rare reports of INR increased in patients treated concomitantly with LC and coumarinic drugs. However, an appropriate sentence has been added in the product information documents (section DDI of SmPC and PIL).

SVII.3.2. Presentation of the missing information

Missing information: Reproductive and congenital toxicity	
Evidence source(s) and strength of evidence	Module 2.5 dated January 27th, 2017.
Anticipated risk/consequence of the missing information	There is no experience of carnitine use in pregnant patients with primary or secondary carnitine deficiency. 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 slight and statistically insignificant greater number of post implantation losses at the highest dose tested (600 mg/kg daily) as compared with control animals. Taking into account the low magnitude of the change and the lack of statistical significance, the biological relevance of these findings to humans is to be considered low. 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. All pregnant women who will become known to the MAH will be followed up for further characterisation.

Potential harm from overdose

Eight cases of overdose were reported post marketing from spontaneous sources, six of which without and two with adverse events. There have been no reports of toxicity from LC overdose (see Module 2.5 dated January 27th, 2017).

Nevertheless, high doses and long-term administration of LC have been associated with diarrhoea (Bain *et al*, 2006a; Löster *et al*, 1999).

No cases of abuse were reported. Given its PK and PD properties, levocarnitine shows no potential for abuse.

Potential for risks resulting from medication errors

Description of medication errors during the clinical trial programme

In the design of the product packaging and labelling, the MAH, when making the new packaging for Alfasigma, will pay attention to prevent errors due to wrong doses by using different colours for the different strengths and errors due to wrong route of administration by indicating very clearly the route of administration.

Reports of medication errors with the marketed product(s)

Six cases of medication error (3 for the oral formulations, 2 for IV formulation, 1 for unknown formulation), of which 2 serious, were collected post marketing from spontaneous sources (see Module 2.5 dated January 27th, 2017). These cases concern wrong route of administration (3) wrong dose (1) off-label use (2).

No safety concern has been identified for medication errors.

Potential for transmission of infectious agents

No potential transmission of infectious agents has been observed or is foreseen for the product.

Potential for off-label use

A total of 28 unexpected cases have been reported for off-label use in post-marketing from spontaneous sources: three cases with IV formulations, 24 cases with oral formulations, 1 with other or unknown formulations.

Most of these cases were reported in an Observational study conducted in Japan where, the LC treatment has been used for unknown indication (8 cases), in other 8 cases LC has been utilized in diseases where there are many scientific literature reports: fibromyalgia (3 cases), malaise -asthenia (2 cases), mitochondrial myopathy (1 case), chronic fatigue (1 case) and muscle weakness (1 case).

Then in five cases LC treatment has been utilized in diseases of musculoskeletal and connective tissue disorders, in three cases for weight control and in other three cases for mesotherapy, slight anaemia, and milk allergy (1 case for each indication).

In one patient, LC was administered as supportive therapy for leukemia and lymphoblastic lymphoma (US-SIGMATAU-ST2015.0216).

Twenty-one out of the 28 patients with a report of off-label use experienced an adverse event. Approximately, two-third of these events were non serious. Among the five patients who experienced a

serious adverse event, only one was really clinically important (pulmonary embolism) but occurred in the patient treated with LC as supportive treatment for leukemia and lymphoblastic lymphoma and was judged not related.

Based on these reported adverse events, the conclusion is that there appear to be no specific safety concern related to off-label use.

Potential for misuse for illegal purposes

Only one non-serious case of drug intentional misuse has been reported for the product. No safety concern regarding potential for misuse for illegal purposes has been evidenced, or foreseen.

Specific Paediatric issues

Issues identified in paediatric investigation plans

No paediatric investigation plan (PIP) is available for LC.

Various formulations of the product are indicated for use in paediatric population and therefore usage in paediatric population falls within the usual remit of use of the product.

Potential for paediatric off-label use

Use in paediatric population is authorized for primary and secondary carnitine deficiencies. Among the 28 cases of off-label use, four were children between 7 months and 11 years (for a few patients age was missing). Out of these four children, one (female) had no ADR, while the remaining three (all males) had the following ADRs: Blood glucose increased, Diarrhea, Eyelid oedema. We can conclude that no specific safety concern related to off-label use in targeted paediatric population was observed.

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Hypersensitivity to levocarnitine or any of its excipients (in particular sucrose and sorbitol, which are contained within some oral formulations of levocarnitine (1.5 g/5 mL, bottles of 20 or 40 mL and Chewable tablets 1 g) and para-hydroxy-benzoates (methyl para-hydroxy-benzoates and propyl para-hydroxy-benzoates), which are contained in the oral formulation (1 g/10 mL and 1.5 g/5 mL). • Accumulation of potentially toxic metabolites trimethylamine (TMA) and trimethylamine-N-oxide (TMAO) in patients with severe renal impairment (oral formulations).
Important potential risks	• Increased incidence and/or severity of seizure attacks in patients with previous seizure activity or underlying predisposing conditions. • Hypoglycaemia in diabetic patients receiving either insulin or hypoglycaemic oral treatment (interaction). • Increased anticoagulant effect of Coumarinic drug (interaction).
Missing information	• Reproductive and congenital toxicity.

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Safety concern 1: Hypersensitivity to levocarnitine or any of its excipients		
Areas requiring confirmation or further investigation	**Proposed routine and additional PhV activities**	**Objectives**
None	Routine Pharmacovigilance	ADRs coded to the MedDRA System Organ Class "Hypersensitivity" and "Allergic reactions" are put under intensive monitoring. Hypersensitivity SMQ and Anaphylactic/ Anaphylactoid Shock Conditions SMQ are considered, in order to establish reporting frequency over time.

Safety concern 2: Accumulation of potentially toxic metabolites trimethylamine and trimethylamine-N-oxide in patients with severe renal impairment (oral formulations)		
Areas requiring confirmation or further investigation	**Proposed routine and additional PhV activities**	**Objectives**
None	Routine Pharmacovigilance	ADRs coded to the MedDRA System Organ Class "Nervous System Disorders" and "Neoplasms benign, malignant and unspecified (incl cysts and polyps)" are put under intensive monitoring.

Safety concern 3: Increased incidence and/or severity of seizure attacks in patients with previous seizure activity or underlying predisposing conditions		
Areas requiring confirmation or further investigation	**Proposed routine and additional PhV activities**	**Objectives**
None	Routine Pharmacovigilance	ADRs coded to the MedDRA Preferred Terms "Seizure" are put under intensive monitoring in order to establish reporting frequency over time.

Safety concern 4: Hypoglycaemia in diabetic patients receiving either insulin or hypoglycaemic oral treatment		
Areas requiring confirmation or further investigation	**Proposed routine and additional PhV activities**	**Objectives**
None	Routine Pharmacovigilance	ADRs occurred in diabetic patients coded to the MedDRA Preferred Terms "Hypoglycaemia" are put under intensive monitoring.

Safety concern 5: Increased anticoagulant effect of Coumarinic drug (interaction)		
Areas requiring confirmation or further investigation	**Proposed routine and additional PhV activities**	**Objectives**
None	Routine Pharmacovigilance	To identify ADRs coded to the MedDRA Preferred Terms "Drug interaction" (with focus on interactions with coumarinic drugs), in order to establish reporting frequency over time.

Safety concern 6: Reproductive and congenital toxicity		
Areas requiring confirmation or further investigation	**Proposed routine and additional PhV activities**	**Objectives**
None	Routine Pharmacovigilance	All ADRs occurring in pregnant women as well as breastfeeding and "Foetus toxicity" are put under intensive monitoring.

III.2 Additional pharmacovigilance activities

No additional pharmacovigilance activities such as non-clinical, clinical or epidemiological (non-interventional or interventional) studies are needed.

III.3 Summary Table of additional Pharmacovigilance activities

Not applicable.

Part IV: Plans for post-authorisation efficacy studies

The main indications of Levocarnitine are primary and secondary deficiencies of carnitine. Carnitine deficiency may occur as a primary metabolic defect or secondary to other inborn error of metabolism, disease conditions, or iatrogenic causes.

No gaps in knowledge about efficacy in the target population have been evidenced; therefore, there is no need for further efficacy post-authorisation studies.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

V.1 Routine Risk Minimisation Measures

Important identified risks

Safety concern 1	**Hypersensitivity to levocarnitine or any of its excipients**
Objective(s) of the risk minimisation measures	To inform patient and HCP on the risk and to minimize it.
Routine risk minimisation measures	Text in CCSI: L-carnitine is contraindicated in case of known hypersensitivity to the active principle or the excipients (section 4.3). Section 4.4 reports a warning (applicable to L-carnitine formulations containing sucrose or sorbitol) that patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase isomaltase insufficiency should not take this medicine. Section 4.4 reports another warning (for the l-carnitine formulations containing para-hydroxy-benzoates (methyl para-hydroxy-benzoates and propyl para-hydroxy-benzoates)): it states that these may cause allergic reactions (possibly delayed). Finally, the events "Rash", Pruritus" and "Injection site reactions" are listed in section 4.8.
	An appropriate sentence according to QRD template and aligned to the CCSI has been included in the SmPC and PIL. The revised texts are going to be submitted to the various Health Authorities for approval and they have been already approved by AIFA.
Additional risk minimisation measure(s) (repeat as necessary)	Not needed.

Safety concern 2	**Accumulation of potentially toxic metabolites trimethylamine and trimethylamine-N-oxide in patients with severe renal impairment (oral formulations)**
Objective(s) of the risk minimisation measures	To inform patient and HCP on the risk and to minimize it.
Routine risk minimisation measures	Text in CCSI: An appropriate sentence according to QRD template and aligned to the CCSI has been included in the SmPC. Under Special populations, in section 4.2, it is said that "Patients with severe renal impairment should not be given high oral doses of levocarnitine for long periods, because of the accumulation of the metabolites trimethylamine and trimethylamine-N-oxide". A warning in section 4.4 is also present.
	All SmPCs will be aligned to the CCSI. The revised texts are going to be submitted to the various Health Authorities for approval and they have been already Approved by AIFA.
Additional risk minimisation measure(s) (repeat as necessary)	Not needed.

Important potential risks

Safety concern 3	**Increased incidence and/or severity of seizure attacks in patients with previous seizure activity or underlying predisposing conditions**
Objective(s) of the risk minimisation measures	To inform patient and HCP on the risk and to minimize it.
Routine risk minimisation measures	Text in CCSI: Section 4.4 reports the following warning: *In patients with previous seizure activity, LC treatment can increase the incidence and/or severity of the seizure attacks. In patients with underling predisposing conditions, LC treatment could trigger the convulsive crisis*. In addition, "Convulsion" is listed in Section 4.8.
	All SmPCs/PILs will be aligned to the CCSI. The revised texts are going to be submitted to the various Health Authorities for approval and they have been already submitted to AIFA.
Additional risk minimisation measure(s) (repeat as necessary)	Not needed.
Safety concern 4	**Hypoglycaemia in diabetic patients receiving either insulin or hypoglycaemic oral treatment**

Safety concern 3	**Increased incidence and/or severity of seizure attacks in patients with previous seizure activity or underlying predisposing conditions**
Objective(s) of the risk minimisation measures	To inform patient and HCP on the risk and to minimize it.
Routine risk minimisation measures	Text in CCSI: Diabetic population is described in section 4.2, as a Special population. Section 4.4 reports the following warning: In diabetic patients receiving insulin or oral hypoglycemic agents, use of L-carnitine may result in hypoglycemia. Regular monitoring of plasma glucose levels is advised in these patients.
	All SmPCs/PILs will be aligned to the CCSI. The revised texts are going to be submitted to the various Health Authorities for approval and they have been already approved by AIFA.
Additional risk minimisation measure(s) (repeat as necessary)	Not needed.

Safety concern 5	**Coumarinic drug interactions (increased anticoagulant effect)**
Objective(s) of the risk minimisation measures	To inform patient and HCP on the risk and to minimize it.
Routine risk minimisation measures	Text in CCSI: Warning in section 4.4 and 4.5 on the augment of anticoagulant effects. It is recommended that the International Normalised Ratio (INR), or other appropriate tests of coagulation, should be monitored weekly until they become stable, and monthly thereafter, in patients taking L-Carnitine with coumarinic drugs.
	All SmPCs/PILs are aligned to the CCSI.
Additional risk minimisation measure(s) (repeat as necessary)	Not needed.

Missing information

Safety concern 6	R**eproductive and congenital toxicit**y
Objective(s) of the risk minimisation measures	To inform patient and HCP on the risk and to minimize it.
Routine risk minimisation measures	Text in CCSI: Section 4.6 reports a warning for pregnancy (L-carnitine should be administered during pregnancy if the benefit for the mother outweighs the potential risks for the foetus.) and one for lactation (L-carnitine should only be used by nursing mothers if benefit to the mother outweighs any potential risks to the child from excess carnitine exposure).
	All SmPCs/PILs will be aligned to the CCSI. The revised texts are going to be submitted to the various Health Authorities for approval and they have been already approved by AIFA.
Additional risk minimisation measure(s) (repeat as necessary)	Not needed.

V.2 Additional Risk Minimisation Measures

There is no need for additional risk minimisation activities because the routine risk minimisation activities, as described in Part V.1, are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of risk minimisation measures

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	**Risk minimisation measures**	**Pharmacovigilance activities**
Safety concern 1: Hypersensitivity to levocarnitine or any of its excipients	Routine risk minimisation measures: SmPC sections 4.3, 4.4, and 4.8. PL section 2. Do not take L-Carnitine, 2. Warnings and Precautions, 4. Possible side effects. Additional risk minimization measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Intensive monitoring. Additional pharmacovigilance activities: None.
Safety concern 2: Accumulation of potentially toxic metabolites	Routine risk minimisation measures: SmPC sections 4.2 and 4.4.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Safety concern	Risk minimisation measures	Pharmacovigilance activities
trimethylamine and trimethylamine-N-oxide in patients with severe renal impairment (oral formulations)	PL section 3. How to take L-carnitine, 2. Warnings and Precautions. Additional risk minimization measures: None.	Intensive monitoring. Additional pharmacovigilance activities: None.
Safety concern 3: Increased incidence and/or severity of seizure attacks in patients with previous seizure activity or underlying predisposing conditions	Routine risk minimisation measures: SmPC sections 4.4 and 4.8. PL section 2. Warnings and Precautions, 4. Possible side effects. Additional risk minimization measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Intensive monitoring. Additional pharmacovigilance activities: None.
Safety concern 4: Hypoglycaemia in diabetic patients receiving either insulin or hypoglycaemic oral treatment	Routine risk minimisation measures: SmPC sections 4.2 and 4.4. PL section 3. How to take L-carnitine, 2. Warnings and Precautions. Additional risk minimization measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Intensive monitoring. Additional pharmacovigilance activities: None.
Safety concern 5: Coumarinic drug interactions (increased anticoagulant effect)	Routine risk minimisation measures: SmPC sections 4.4 and 4.5. PL section 2. Warnings and Precautions, 2. Other medicines and L-Carnitine. Additional risk minimization measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Intensive monitoring. Additional pharmacovigilance activities: None.
Safety concern 6: Reproductive and congenital toxicity	Routine risk minimisation measures: SmPC section 4.6. PL section 2. Pregnancy, breast feeding and lactation.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Intensive monitoring.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Additional risk minimization measures: None.	Additional pharmacovigilance activities: None.

Part VI: Summary of the risk management plan

Summary of risk management plan for <Tradename>

This is a summary of the risk management plan (RMP) for <Tradename>. The RMP details important risks of <Tradename>, how these risks can be minimised, and how more information will be obtained about <Tradename>’s risks and uncertainties (missing information).

<Tradename>'s summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how <Tradename> should be used.

I. The medicine and what it is used for

<Tradename> is authorised for various indications worldwide and the most common ones are primary and secondary carnitine deficiencies (see SmPC for the full indication). It contains carnitine as the active substance and it is given by the following oral formulations:

- oral solution 1 g/10 mL
- oral solution 2 g/10 mL
- chewable tablets 1 g
- tablets 330 mg
- 1.5 g/5 mL oral solution (oral solution 30%, bottles of 40 mL)
- 1.5 g/5 mL oral solution (oral solution 30%, bottles of 20 mL)

or by the following injectable formulations:

- solution for injection 1 g/5 mL
- solution for injection 2 g/5 mL
- 1 bag solution for infusion 1 g/100 mL with sodium chloride
- 1 bag solution for infusion 2.5 g/250 mL with sodium chloride
- solution for infusion 1 g/100 mL with glucose
- solution for infusion 2.5 g/250 mL with glucose.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of <Tradename>, together with measures to minimise such risks and the proposed studies for learning more about <Tradename>'s risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine’s packaging;

- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

If important information that may affect the safe use of <Tradename> is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of <Tradename> are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of <Tradename>. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	• Hypersensitivity to <Tradename> or any of its excipients (in particular sucrose and sorbitol, which are contained within some oral formulations of <Tradename> (1.5 g/5 mL, bottles of 20 or 40 mL and Chewable tablets 1 g) and para-hydroxy-benzoates (methyl para-hydroxy-benzoates and propyl para-hydroxy-benzoates), which are contained in the oral formulation (1 g/10 mL and 1.5 g/5 mL)). • Accumulation of potentially toxic metabolites trimethylamine (TMA) and trimethylamine-N-oxide (TMAO) in patients with severe renal impairment (oral formulations).
Important potential risks	• Increased incidence and/or severity of seizure attacks in patients with previous seizure activity or underlying predisposing conditions. • Hypoglycaemia in diabetic patients receiving either insulin or hypoglycaemic oral treatment (interaction)**.** • Increased anticoagulant effect of Coumarinic drug (interaction).
Missing information	• Reproductive and congenital toxicity.

II.B Summary of important risks

Important identified risk: Hypersensitivity to levocarnitine or any of its excipients	
Evidence for linking the risk to the medicine	Nine events of local reactions ("Rash" (2), "Pruritus" (2), and "Injection site reactions" (5)) were collected in a total of 1636 patients treated in levocarnitine sponsored studies. In addition, 25 events of "Rash" and 22 of "Pruritus" were collected in post-marketing. Few systemic reactions with cardiovascular and/or respiratory involvement, all classifiable as mild to moderate systemic reactions, were observed in post-marketing.
Risk factors and risk groups	Patients with history of <Tradename> hypersensitivity. Patients with fructose intolerance, glucose-galactose malabsorption, or sucrase-isomaltase insufficiency.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.3, 4.4, and 4.8. PL section 2. Do not take <Tradename>, 2. Warnings and Precautions, 4. Possible side effects.
Important identified risk: Accumulation of potentially toxic metabolites trimethylamine (TMA) and trimethylamine-N-oxide (TMAO) in patients with severe renal impairment (oral formulations)	
Evidence for linking the risk to the medicine	Carnitine and its metabolites are eliminated from the body mainly via urinary excretion (Evans, 2003). It follows that chronic administration of oral <Tradename> to patients with severely compromised renal function, or in end stage renal disease (ESRD) and on dialysis may result in accumulation of TMA and TMAO, which can cause carcinogen and neurological toxicity potential. The extent of the accumulation of these metabolites has been investigated in six patients with ESRD undergoing haemodialysis following oral administration of <Tradename> 1 g daily for 12 days (Bain *et al*, 2006b). Although plasma levels of TMA remained unaltered, pre-dialysis plasma concentrations of TMAO increased significantly and continued to rise during the study.
Risk factors and risk groups	Patients with severely compromised renal function or ESRD patients on dialysis, who require chronic administration of high doses of <Tradename>.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.2 and 4.4. PL section 3. How to take <Tradename>, 2. Warnings and Precautions.
Important potential risk: Increased incidence and/or severity of seizure attacks in patients with previous seizure activity or underlying predisposing conditions	

Evidence for linking the risk to the medicine	Almost all reported seizure cases regarded patients with previous seizure activity or with underlying predisposing conditions. Therefore, the risk concerning seizure has been formulated as follows: "In patients with previous seizure activity, <Tradename> treatment can increase the incidence and/or severity of the seizure attacks. In patients with underling predisposing conditions, <Tradename> treatment could trigger the convulsive crisis".
Risk factors and risk groups	Patients taking levocarnitine who have a pre-existing history of seizures or having underlying predisposing conditions.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.4 and 4.8. PL section 2. Warnings and Precautions, 4. Possible side effects.
Important potential risk: Hypoglycaemia in diabetic patients receiving either insulin or hypoglycaemic oral treatment (interaction)	
Evidence for linking the risk to the medicine	Improving the utilisation of glucose, <Tradename> may induce hypoglycaemic state in presence of exogenous insulin or use of hypoglycaemic drugs.
Risk factors and risk groups	Patients treated for diabetic disease.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.2 and 4.4. PL section 3. How to take <Tradename>, 2. Warnings and Precautions.
Important potential risk: Increased anticoagulant effect of Coumarinic drug (interaction)	
Evidence for linking the risk to the medicine	<Tradename> might increase the effect of coumarinic drugs and might slow blood clotting too much. The final result can be an increased risk of uncontrolled bleeding. There have been very rare reports of INR (International Normalised Ratio) increase in patients treated concomitantly with <Tradename> and cumarinic drugs for which the effect of an interaction between <Tradename> and coumarinic drugs could not be excluded. No interaction was observed in rats between <Tradename> and warfarin on prothrombin time, and no significant biological plausibility was ascertained from the examined literature.
Risk factors and risk groups	Patients receiving anticoagulant treatment with coumarinic drugs.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.4 and 4.5.

	PL section 2. Warnings and Precautions, 2. Other medicines and <Tradename>.
Missing information: Reproductive and congenital toxicity	
Risk minimisation measures	<u>Routine risk minimisation measures:</u> SmPC section 4.6. PL section 2. Pregnancy, breast feeding and lactation.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of <Tradename>.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for <Tradename>.

Part VII: Annexes

Table of contents

Annex 1 – EudraVigilance Interface

Not Applicable

Annex 2 – Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme

Not Applicable

Annex 3 - Protocols for proposed, on-going and completed studies in the pharmacovigilance plan

Not Applicable

Annex 4 - Specific adverse drug reaction follow-up forms

Not Applicable

Annex 5 - Protocols for proposed and on-going studies in RMP part IV

Not Applicable

Annex 6 - Details of proposed additional risk minimisation activities (if applicable)

Not Applicable

Annex 7 - Other supporting data (including referenced material)

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Annex 8 – Summary of changes to the risk management plan over time

Major changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment for change
1 [redacted]	01/12/2012	*Important Identified Risks* Accumulation of potentially toxic metabolites in patients with renal insufficiency	Unchanged
		Use in patients with fructose intolerance, glucose-galactose malabsorption and sucrose-isomaltase insufficiency	Combined with Hypersensitivity to levocarnitine or any of its excipients
		Reproductive and congenital toxicities in pregnant/lactating females	Moved under missing information
		Mild GI complaints and body odour	Not considered an important identified risk
		Interaction with insulin or oral hypoglycaemic treatment in patients with diabetes	Unchanged
		Hypersensitivity to levocarnitine or any of its excipients	See above
		Off-label use	No safety issue or potential risk has been highlighted for the off label use
		Overdose	Given its PK and PD properties, levocarnitine shows no potential for abuse.
		Medication errors	No safety concern has been identified about potential for medication error
		Potential Risks Seizures.	Better defined
		• Coumarinic drug interactions	Unchanged
		Missing information Elderly	This RMP referred only to the paediatric formulation. Not applicable for LC when considering all formulations.

Version	Date	Safety Concerns	Comment for change
2	23/10/2017	*Identified Risks* Hypersensitivity to levocarnitine or any of its excipients (anaphylactic shock) Accumulation of potentially toxic metabolites trimethylamine and trimethylamine-N-oxide in patients with severe renal impairment (oral formulations) *Potential Risks* Increased incidence and/or severity of seizure attacks in patients with previous seizure activity or underlying predisposing conditions Hypoglycaemia in diabetic patients receiving either insulin or hypoglycaemic oral treatment (interaction) Increased anticoagulant effect of Coumarinic drug (interaction) *Missing Information* Reproductive and congenital toxicities in pregnant/lactating females	Based on update of safety part of Module 2.5 dated January 27th, 2017

The following risks were present in the previous version of the RMP and categorized in the same way (i.e. important identified risks or important potential risks):

- Accumulation of potentially toxic metabolites trimethylamine (TMA) and trimethylamine-N-oxide (TMAO) in patients with severe renal impairment (oral formulations).
- Hypoglycaemia in diabetic patients receiving either insulin or hypoglycaemic oral treatment (interaction).
- Increased anticoagulant effect of coumarinic drug (interaction).

The following risks were also present in the previous version of the RMP and categorized in the same way; however, in the new version of the RMP they have been formulated more accurately:

- Hypersensitivity to levocarnitine or any of its excipients (in particular sucrose and sorbitol, which are contained within some oral formulations of levocarnitine (1.5 g/5 mL, bottles of 20 or 40 mL and Chewable tablets 1 g) (previous version of the RMP was only focused on sucrose and sorbitol)).
- Increased incidence and/or severity of seizure attacks in patients with previous seizure activity or underlying predisposing conditions (previous version of the RMP only mentioned Seizure).

Reproductive and congenital toxicity, which was reported as a potential risk in the previous version of the RMP, has been now reported as missing information.

"Mild gastrointestinal complaints and body odor", which were reported as a potential risk in the previous version of the RMP, has been dropped because this is not considered an important potential risk.

Finally, the potentials for off-label use, medication errors and overdose have been removed based on the evidence of the collected data.