Recommendation No. 17/2020

of 10 February 2020

issued by the President of the Agency for Health Technology Assessment and Tariff System

on whether L-carnitine (a foodstuff for particular nutritional uses) should be reimbursed in the following indications: under the drug programme: "Adjuvant therapy using L-carnitine in the following indications: 3-Methylcrotonylglycinuria – MCC, glutaric acidemia type 1 – GA I, isovaleric acidemia – IVA, methylmalonic acidemia – MMA, propionic acidemia – PA, long-chain fatty-acid oxidation disorders – LC-FAOD, medium-chain acyl-CoA dehydrogenase deficiency – MCADD, carnitine uptake defect – CUD, multiple acyl-CoA dehydrogenation deficiency – MADD (E 71.1, E 71.3, E 72.3)"

The President of the AOTMiT does not recommend reimbursing the following foodstuff for particular nutritional uses:

- L-carnitine, powder, 50 x 1 g. EAN: 5016533045017,

indicated in: treatment under the following drug programme: "Adjuvant therapy using L-carnitine in the following indications: 3-Methylcrotonylglycinuria – 3-MCC, glutaric acidemia type 1 – GA I, isovaleric acidemia – IVA, methylmalonic acidemia – MMA, propionic acidemia – PA, long-chain fatty-acid oxidation disorders – LC-FAOD, medium-chain acyl-CoA dehydrogenase deficiency – MCADD, carnitine uptake defect – CUD, multiple acyl-CoA dehydrogenation deficiency – MADD (E 71.1, E 71.3, E 72.3)".

Statement of reasons for the recommendation

The President of the AOTMiT, taking into account the position of the Transparency Council and the available scientific evidence, as well as the results of pharmacoeconomic analyses and clinical guidelines, has concluded that financing of the health technology in question from public funds is not justified.

The main limitation of the efficacy and safety analysis is the lack of high-quality evidence – RTCs concerning the technology in question.

Therefore, an assessment of the efficacy and safety of L-carnitine in the indications in question is based on lower-class scientific evidence (non-randomised single-arm studies, case series and individual case

studies). In total, 10 single-arm studies, 17 case series and 34 individual case studies on the use of L-carnitine in the analysed populations were included in the analysis. Taking into account the rare nature of the indications in question,it is unlikely that RCTs will ever be performed, however drawing any conclusions based on the results obtained in individual patients with specific diagnoses is, in the opinion of the President of the AOTMiT, an overly far-reaching generalisation.

It should be noted that scientific evidence concerning the efficacy of L-carnitine in the indications in question is inconsistent. For the following indications: Methylmalonic acidemia (MMA), propionic acidemia (PA), long-chain 30hydrocyacyl-CoA dehydrogenase deficiency (LCHAD), carnitine-acylcarnitine translocase (CACT), carnitine uptake defect (CUD), multiple acyl-CoA dehydrogenation deficiency (MADD), the results of the studies indicate positive effects of the applied therapeutic treatment, which included supplementation of L-carnitine in terms of the influence on the normalisation of carnitine levels in the blood, the increase of excretion of harmful metabolites from the body and the improvement of the patients' clinical condition.

However, for the indications concerning: 3-methylcrotonylglycinuria (3-MCC), glutaric acidemia type 1 (GA I), isovaleric acidemia (IVA), very long-chain acyl-CoA dehydrogenase deficiency (VLCADD), medium-chain acyl-CoA dehydrogenase deficiency (MCADD), mitochondrial trifunctional protein deficiency (MTP) and carnitine palmitoyltransferase 2 (CPT2), results on the efficacy of L-carnitine are inconclusive.

It is also worth mentioning that most of the identified studies did not assess the safety profile of L-carnitine. In those studies where information on the safety of L-carnitine was presented, the main adverse effects associated with treatment are hyperglycaemia (Berry 1988), while in some patients, hepatic impairment was observed (Hoffmann 1996). Furthermore, the most frequently reported reactions were weight gain, intestinal disorders and bad body odour (Rasmussen 2014, Thomsen 2014)

According to the results of the economic analysis conducted using cost-minimisation, the annual total cost of using L-carnitine *[information protected as a trade secret]*, the annual cost under the targeted import procedure amounts to PLN 22,300.00. Introduction of the proposed drug programme would reduce the annual expenditure on treatment per patient by PLN 7,000.00, taking into account only the costs of the drug; however, this analysis is limited by the fact that the sensitivity analysis assessed only the impact of L-carnitine consumption on results of the economic analysis; the impact of other parameters, i.e. the impact of alternative costs of inclusion in the programme, diagnostics or monitoring of treatment efficiency, has not been tested, which, to some extent, limits the possibility of drawing conclusions from the presented analysis.

The results of the budget impact analysis indicate that if a positive reimbursement decision regarding L-carnitine under the drug programme was to be taken instead of importing it under the targeted import procedure, one should anticipate savings for the public payer (NHF) at the level of *[information protected as a trade secret]* per year. The presented savings result from a reduction in the cost of L-carnitine; however, it should be noted that the costs associated with including the patients in the drug programme and monitoring its efficacy should be expected to increase (similarly as in the case of interpretation of economic analysis results). *[information protected as a trade secret].*

Subject of the application

The order of the Minister of Health concerns assessing whether the following foodstuff for particular nutritional uses should be reimbursed:

- L-carnitine, powder, 50 x 1 g. EAN: 5016533045017 with the net ex-factory price of PLN ***[information protected as a trade secret];***

indicated in: treatment under a drug programme: "Adjuvant therapy using L-carnitine in the following indications: 3-Methylcrotonylglycinuria – 3-MCC, glutaric acidemia type 1 – GA I, isovaleric acidemia – IVA, methylmalonic acidemia – MMA, propionic acidemia – PA, long-chain fatty-acid oxidation

disorders – LC-FAOD, medium-chain acyl-CoA dehydrogenase deficiency – MCADD, carnitine uptake defect – CUD, multiple acyl-CoA dehydrogenation deficiency – MADD (E 71.1, E 71.3, E 72.3)".

The proposed reimbursement availability category – drug available as part of a drug programme. The proposed patient co-payment level – free-of-charge. The drug would be financed under a new limit group. No risk-sharing scheme was proposed.

Health problem

3-methylcrotonyl-Coenzyme A carboxylase deficiency, MCC/3-MCCD

3-methylcrotonyl-Coenzyme A carboxylase deficiency, ICD-10 E71.1, is an inherited leucine metabolism disorder. It is a rare disease characterised by a variable clinical presentation – a metabolic breakthrough may occur during infancy, whereas in adults, an asymptomatic form is possible. It is a rare disease, its prevalence in Europe is estimated at: 1:50,000–1:30,000. It is worth mentioning that, in the case of the indication in question and the indications presented below, due to the fact that they belong to rare diseases, no precise, separate epidemiological data for Poland is available.

Glutaric acidemia type-1, GA I

Glutaric acidemia type-1, ICD-10 E71.3, also referred to as glutaryl-Coenzyme A dehydrogenase deficiency, GDD, is a rare neurometabolic disorder inherited in an autosomal recessive fashion. It is characterised by acute encephalopathy episodes which result in damage to the striatum and serious movement disorders in the form of dystonia and dyskinesia. It is a rare disease, its prevalence is estimated at: 1:40,000-1:80,000.

Isovaleric acidemia, IVA

Isovaleric acidemia, IVA, ICD-10 E71.1, is an organic acidemia inherited in an autosomal recessive fashion, characterised by a deficiency of isovaleryl-CoA dehydrogenase and high clinical variability. The disease can present itself in infancy through acute symptoms such as vomiting, poor weight gain, convulsions, lethargy, the characteristic smell of "sweaty feet", acute pancreatitis, mild to severe developmental retardation or in childhood through metabolic acidosis (caused by prolonged starvation, increased supply of protein-rich foods or infections). The prevalence of isovaleric acidemia is estimated at 1:80 000-1:100 000 births.

Methylmalonic aciduria, MMA

Methylmalonic aciduria, MMA, ICD-10 E71.1, is a metabolic block derived from methylmalonic acid. Methylmalonic acid is derived from the catabolism of isoleucine and valine. There are many variants of methylmalonic aciduria. Most often, it is caused by a defect in activation of vitamin B12 into enzyme form or enzymatic defect of methylmalonyl-CoA mutase converting methylmalonyl-CoA to succinyl-CoA. MMA belongs to the group of congenital metabolic defects associated with an increased level of methylmalonic acid in blood and urine without hyperhomocyteinemia or homocystinuria. The concentration of methylmalonic acid in seriously affected patients is significantly increased in serum, urine and cerebrospinal fluid. The disease is inherited in an autosomal recessive fashion. The prevalence of methylmalonic aciduria is estimated at 1:80,000-1:100,000 births.

Propionic acidemia, PA

Propionic acidemia, ICD-10 E71.1, also referred to as propionic acidosis, is an organic acidosis caused by a deficit of propionyl-CoA carboxylase. The disease is characterised by life-threatening episodes of metabolic decompensation, neurological disorders and cardiomyopathy. The prevalence of the disease is estimated at 1:50,000-1:100,000 live births worldwide.

LONG-CHAIN FATTY-ACID OXIDATION DISORDERS (LC-FAOD)

Fatty acid oxidation disorders is a group of congenital metabolic diseases which lead to accumulation of fatty acids and reduced energy metabolism of cells. Every fatty acid oxidation disorder is associated

with a specific enzyme defect in the fatty acid metabolic pathway and affects the usage of dietetic and stored fat.

The following fatty acid oxidation disorders have been taken into account within the framework of the drug programme in question:

3-hydroxyacyl-CoA dehydrogenase deficiency (LCHADD) and mitochondrial trifunctional protein deficiency (MTP) – ICD-10: E71.3 are mitochondrial beta-oxidation disorders of long-chain fatty acids. Trifunctional mitochondrial protein deficiency is extremely rare – less than a hundred cases of this disease have been described in literature. In the opinion of the clinical expert *[information protected as a trade secret],* in Poland, *[information protected as a trade secret] with the MTP diagnosis.*

Very long-chain acyl-coa dehydrogenase deficiency, VLCADD – ICD-10: E71.3, is an inherited mitochondrial beta-oxidation disorder of long-chain fatty acids. The prevalence of very long-chain L-3 hydroxyacyl-CoA dehydrogenase deficiency in (very) long-chain fatty acids is currently estimated at 1:30,000-1:100,000 births. The literature describes over 400 cases worldwide. The prevalence in Germany is 1:50,000. In the opinion of the clinical expert *[information protected as a trade secret],* the number of patients in Poland diagnosed with VLCADD amounts to *[information protected as a trade secret],* of which *[information protected as a trade secret]* qualify for L-carnitine treatment *([information protected as a trade secret]).*

Carnitine-acylcarnitine translocase deficiency, CACT – ICD-10: E71.3 is a disorder of beta-oxidation of fatty acids. Carnitine-acylcarnitine translocase deficiency is an extremely rare condition. Less than 60 cases have been described worldwide. In the opinion of the clinical expert *[information protected as a trade secret]* the number of patients in Poland with CACT diagnosis amounts to *[information protected as a trade secret].*

Carnitine palmitoyl transferase type 2 deficiency, CPT 2D – ICD-10: E71.3, is caused by a deficiency of carnitine palmitoyltransferase 2 enzyme in fibroblasts or leukocytes. The prevalence of carnitine palmitoyl transferase type 2 deficiency is estimated at approx. 1:300,000; the disease is more common in young men. Approx. twenty families with lethal neonatal form and approx. 28 families with acute hepatic and myocardial forms have been described. Results for over 300 cases of the myopathic form of CPT II deficiency have been published. Symptoms of the myopathic form may be mild and physical impairment might not occur; therefore, this form of CPT II deficiency may be underestimated. In the opinion of the clinical expert *[information protected as a trade secret]* the number of patients in Poland with the CPT II diagnosis *[information protected as a trade secret].*

Medium chain acylCoA dehydrogenase, MCADD – ICD-10: E71.3, is an inherent defect in the mitochondrial oxidation of fatty acids. The estimated prevalence of medium chain acylCoA dehydrogenase ranges from 1: 4,900 to 1:27,000 births in the white population and is highest in people of Northern European origin. The prevalence of this disease is 1:14,600 births worldwide. In the opinion of the clinical expert *[information protected as a trade secret]* the number of patients in Poland with MCADD diagnosis amounts to *[information protected as a trade secret],* of which *[information protected as a trade secret]* qualify for L-carnitine treatment *([information protected as a trade secret]).*

Carnitine uptake deficiency, CUD / Primary carnitine deficiency, PCD – ICD-10: E71.3, is a life-threatening fatty acid oxidation disorder. The prevalence of carnitine uptake deficiency ranges from 1:20,000 to 1:70,000 in the USA, 1:40 000 in Japan and 1:120 000 in Australia. The disease is very common in the Faroe Islands, where its prevalence is 1:300. In the opinion of the clinical expert *[information protected as a trade secret]* the number of patients in Poland diagnosed with CUD is *[information protected as a trade secret].*

Multiple acyl-CoA dehydrogenation deficiency, MADD – ICD-10: E71.3 is a fatty acid and amino acid oxidation disorder. The prevalence of multiple acyl-CoA dehydrogenation deficiency is estimated at 1:200,000 births, however significant differences between countries/ethnic groups are observed. In the opinion of the clinical expert *[information protected as a trade secret]* the number of patients in Poland diagnosed with MADD is *[information protected as a trade secret]*, of which *[information protected as a trade secret]* qualify for L-carnitine treatment.

According to the data received from the Ministry of Health concerning targeted import of L-carnitine, 257 approvals for 80 individual patients were issued between 2017-2019.

Alternative health technologies

According to the identified clinical guidelines and opinions of clinical experts, there is no technology constituting an alternative to L-carnitine in the indications in question.

According to the applicant, no alternative health technologies are available in the indications in question – the alternative is no L-carnitine supplementation.

The applicant adopted L-carnitine financed under the targeted import procedure as the comparator for the purpose of the economic analysis and the public payer budget impact analysis.

In the opinion of the Agency this choice should be deemed justified.

Description of the proposed intervention

According to the applicant's letter to the Chief Sanitary Inspectorate (attached to the application), the following indications for the use of L-carnitine have been registered:

- dietary treatment of diseases requiring an additional supply of L-carnitine as a dietary supplement.

According to the L-carnitine label [E49118Z01] (attached to the application), the drug takes the form of a powder for oral administration and the recommended dose which depends on the age, body weight and clinical condition of the patient must be determined exclusively by the doctor.

Due to their nature, the indications in question, i.e. diseases requiring an additional supply of L-carnitine as a dietary supplement, are included in the marketing authorisation indication.

Efficacy, effectiveness and safety assessment

The assessment consists in the collection of data on health consequences (efficacy and safety) resulting from the use of a new therapy in a given health problem and other publicly financed therapies which constitute an alternative treatment option available in a given health problem. Then, the assessment requires determining the reliability of the collected data and comparing the results regarding the efficacy and safety of the new therapy with those of therapies already available in a given health problem.

Based on the above, the efficacy and safety assessment allows for obtaining information about the extent of the health effect (with regard to both efficacy and safety) to be expected in relation to the new therapy compared to the other considered therapeutic options.

10 single-arm studies, 17 case series and 34 individual case studies have been found as part of the efficacy and safety evaluation of L-carnitine in the analysed indications:

- 3-Methylcrotonylglycinuria (MCC)
    - Thomsen 2014 – prospective, single-arm study designed to assess the response to L-carnitine treatment in a population of adult patients diagnosed with 3-Methylcrotonylglycinuria. Treatment period/observation: 3 months. 13 patients were included and divided into two groups – depending on whether they had received L-

carnitine supplementation prior to the study. Study quality score on the NICE scale – 5/8 points.

- 3 case studies: Kaushal 2010, Lehnert 1996, Rutledge 1995.

- glutaric acidemia type 1 (GA I)
  - Kölker 2006 – international cross-sectional study carried out in 35 metabolic disease treatment centres using standardised questionnaires. No data on the treatment/observation period. Number of patients: 279. The analysis included variables such as diagnostic procedures, dietary treatment, L-carnitine supplementation, riboflavin supplementation, gender, presence of macrocephaly, perinatal complications, socio-economic status of parents, biochemical phenotype, biochemical response to treatment, frequency of monitoring of biochemical parameters.
  - Heringer 2010 – prospective study assessing survival rates, the occurrence of an acute encephalopathic crisis, severity of movement disorders, occurrence of motor disability. 52 patients were included in the study. The mean individual patient observation time was 5.5 years (range: 8 months – 11.5 years). Study quality score on the NICE scale – 4/8 points.
  - Guerreiro 2018 – study to assess the protective effect of L-carnitine on oxidative damages. The median treatment was 2 months (range from 1 to 4 months). Study quality score on the NOS scale – 5 points.
  - 7 case series: Kyllerman 1994, Wang 2013, Strauss 2011, Bijarnia 2008, Kyllermann 2004, Naughten 2004 i Hoffmann 1991.
- isovaleric acidemia, IVA
  - 1 case series: Berry 1998.
  - 1 case study: Chinen 2017.
- Methylmalonic acidemia (MMA)
  - Wang 2018 – retrospective study assessing the effects of L-carnitine on the clinical presentation and treatment effects in the population of patients with methylmalonic acidemia and homocystinuria (cblC).` Treatment period: 2-4 weeks. Observation period: 1-3 years. Study quality score on the NICE scale – 2/8 points.
- propionic acidemia (PA)
  - 1 case study: Bernheim 2017.
- long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHADD)
  - 1 case study: Korenke 2003.
- very long-chain acyl-coa dehydrogenase deficiency (VLCADD)
  - 3 case series: Alsayed 2016, Mohamed 2010, Watanabe 2018.
  - 5 case studies: Fatehi 2018, Doi 2000, Touma 2001, Smelt 1998, Costa 1998.
- mitochondrial trifunctional protein deficiency (MTP)
  - 2 case studies: Miyajima 1999 and Park 2009.
- carnitine-acylcarnitine translocase deficiency (CACT),
  - 1 case series: Vitoria 2014.

  - 1 case study: Iacobazzi 2004.

- carnitine palmitoyl transferase type 2 deficiency (CPT2)
  - 3 case studies: Elpeleg 1993, Fontaine 1998, Hori 2010.
- medium chain acylCoA dehydrogenase (MCADD)
  - Derks 2014 – the influence of L-carnitine on the occurrence of oxidative damages and changes in enzymatic antioxidative mechanisms was assessed. No data on the treatment observation period. Study quality score on the NOS scale – 5 points.
  - Huidekoper 2006 – the effect of L-carnitine in patients with MCADD on prolonged moderate-intensity exercises was assessed. Treatment period: a minimum of 4 weeks. Study quality score on the NICE scale – 4/8 points.
  - Lee 2005 – the effect of L-carnitine on exercise tolerance was assessed. Treatment period: 4 weeks. Study quality score on the NICE scale – 4/8 points.
  - Madsen 2013 – the effect of L-carnitine supplementation on the total fatty acid oxidation rates and the degree of palmitate oxidation. Treatment period: 4 weeks. Study quality score on the NOS scale – 5 points.
  - 1 case study on the use of L-carnitine in a patient with MCADD: Treem 1989.
- carnitine uptake defect (CUD)
  - Madsen 2018 – study assessing metabolism during exercise in patients with a primary carnitine uptake defect with or without L-carnitine supplementation. Treatment period ≥ 3 years. Observation period: 4 days. Study quality score on the NOS scale – 5 points.
  - 3 case series: Rasmussen 2014, Sarafoglou 2010, Vielhaber 2004.
  - 4 case studies: Agnetti 2013, Hou 2002, Yilmaz 2015, Yoon 2012.
- multiple acyl-CoA dehydrogenation deficiency (MADD)
  - 2 case series: Macchione 2018, Angelini 2014.
  - 12 case studies: Rosa 2012, Mandel 1988, Fontaine 1996, Creanza 2017, Ayala 2018, Yamaguchi 1991, Donis 2015, Pietrini 2014, Zhuo 2015, Ishii 2012, Izumi 2011, Liang 2004.

The following parameters were used to assess efficacy and safety:

- MD – mean difference.

Efficacy and effectiveness

In the absence of randomised clinical trials concerning the technology in question efficacy of L-carnitine in the indications in question was assessed based on scientific evidence characterised by the lowest reliability (single-arm studies, case series, case studies). Therefore, this analysis does not include a detailed description of the results of individual studies and instead presents a summary of the results of the scientific evidence found in relation to the indications in question:

- 3-Methylcrotonylglycinuria (MCC)

  In the treatment of patients with 3-methylcrotonylglycinuria, the main interventions included a low-protein diet and L-carnitine supplementation. The obtained data on the efficacy of L-carnitine in normalising the level of carnitine in blood and urine is inconclusive (Thomsen 2014). In some cases, no changes after its administration have been observed (Lehnert 1996, Rutledge 1995).

In conclusion, the identified study and case series indicate ambiguous results concerning the efficacy of L-carnitine in MCC therapy.

- glutaric acidemia type 1 (GA I)

  The conclusions concerning the treatment of glutaric acidemia type I are as follows: early diagnosis and treatment with, i.a. L-carnitine may prevent the development of dystonic and diskinetic disorders associated with glutaric acidemia. Although clinical improvement was not achieved in all patients, that may be related to the delayed treatment implementation and the very advanced condition of the patient, at which point reversing the disease complications becomes impossible.

  In conclusion, the identified studies and case series indicate ambiguous results concerning the efficacy of L-carnitine in GA I therapy.

- isovaleric acidemia, IVA

  An analysis of publications concerning the use of L-carnitine in the population of patients with isovaleric acidemia indicates the efficacy of L-carnitine supplementation in increasing free and total carnitine levels in serum and the carnitine levels in red blood cells. It has also been shown that early treatment initiation in diagnosed infants not experiencing complications allows their proper mental development. No difference was observed in the annual number of episodes of ketoacidosis in patients receiving carnitine, glycine and low-protein diet as compared to patients receiving only glycine and dietary therapy.

  In conclusion, the identified case studies and case series indicate ambiguous results regarding the efficacy of L-carnitine in IVA therapy.

- Methylmalonic acidemia (MMA)

  Efficacy of L-carnitine in the population of patients suffering from methylmalonic acidemia was analysed on the basis of a retrospective analysis of 8 patients with neuropsychiatric symptoms. After 2-4 weeks of treatment, neuropsychiatric symptoms were alleviated in 4 out of 8 patients. An increase in muscle strength was observed in the patients. During 1-3 years of observation, neuropsychiatric and motor symptoms of all patients were alleviated.

  In conclusion, results of the identified study are in favour of the intervention in treatment of MMA, however, conclusions were drawn based on a small patient sample (8 persons), which limits the possibility to conclude about the effects of the therapy.

- propionic acidemia (PA)

  A case study regarding a newborn with bilateral nephromegaly and hyperchogenic changes in the kidney, indicated that an ultrasound test carried out in month 8 of life showed a regression of renal dysfunction.

  In conclusion, results of the identified case study are in favour of the intervention in treatment of LCHADD. However, due to the small clinical sample (single case), it is difficult to determine whether similar effects would be obtained in the entire patient population.

- 3-hydroxyacyl-CoA dehydrogenase deficiency (LCHADD)

  The response to creatine and L-carnitine supplementation in a patient with 3-hydroxyacyl-CoA dehydrogenase deficiency included muscle pain relief, improvement and normalisation of ventricular function (increase in the ejection fraction from 23% to 36%).

  In conclusion, results of the identified case study are in favour of the intervention in treatment of LCHADD, however, the quality of the scientific report is low and the drawn conclusion is based on results obtained in a single patient.

- very long-chain acyl-coa dehydrogenase deficiency (VLCADD)

  The response of patients with very long-chain acyl-coa dehydrogenase deficiency was manifested in improvement of muscle strength (Fatehi 2018), liver size and its functions, reduction of the creatine kinase level (Doi 2000), subsiding of metabolic acidosis episodes with normal growth and development (Touma 2001). There are also reports indicating the lack of efficacy of L-carnitine in this population (Smelt 1998, Watanabe 2018), where no clinical improvement has been achieved after L-carnitine implementation or when such improvement was achieved after discontinuation of L-carnitine administration.

  In conclusion, the identified case studies and case series indicate ambiguous results concerning the efficacy of L-carnitine in treatment of VLCHAD.

- mitochondrial trifunctional protein deficiency (MTP)

  The response to L-carnitine supplementation in an adult patient included muscle pain relief and an increased free carnitine level (surrogate endpoint). High-dose L-carnitine supplementation did not prevent rhabdomyolysis with lactic acidosis during exercise, while a low dose maintained subnormal levels of free carnitine and improved exercise tolerance. In the case of an infant with a severe form of the disease, treatment based on glucose, medium-chain triglyceride diet and L-carnitine supplementation did not prevent advanced heart failure leading to death.

  In conclusion, the identified case studies indicate ambiguous results concerning the efficacy of L-carnitine in treatment of MTP.

- carnitine-acylcarnitine translocase deficiency (CACT),

  In the identified publications concerning L-carnitine supplementation in the population of patients with carnitine-acylcarnitine translocase deficiency, the use of a diet rich in medium-chain fatty acids and carnitine was effective in reversing the clinical symptoms of CACT deficiency and significantly improved the results of acylocarnitine profile tests.

  In conclusion, the identified case studies and case series indicate the results in favour of the intervention in treatment of CACT, however it is difficult to indicate to what extent it was the effect of a properly maintained diet and to what extent it was the effect of L-carnitine supplementation.

- carnitine palmitoyl transferase type 2 deficiency (CPT)

  Implementation of L-carnitine supplementation in patients with carnitine palmitoyl transferase type 2 deficiency resulted in the normalisation of free carnitine level and acyl/free carnitine ratio in the blood (Fontaine 1998, Hori 2010), improvement of the patient's clinical condition, size and function of the liver and echocardiogram results, with the presence of biochemical abnormalities in laboratory tests (Elpeleg 1993).

  In conclusion, the identified case studies indicate ambiguous results concerning the efficacy of L-carnitine in treatment of CPT.

- medium chain acylCoA dehydrogenase (MCADD)

  L-carnitine supplementation in the population of patients with medium chain acylCoA dehydrogenase helps protect the patient's body from oxidative damage (Derks 2014). The authors of the publication recommend further studies to determine the clinical relevance of oxidative stress. Exercise tolerance in MCADD patients can be improved short term through L-carnitine supplementation (Lee 2005, Heidekoper 2006); however, it cannot be excluded

that MCADD patients may also benefit from L-carnitine supplementation during moderate intensity exercise lasting more than 2 hours (Heidekoper 2006). In the analysed case of a single patient (Treem 1989), L-carnitine therapy did not prevent lethargy, vomiting, hypoglycaemia and accumulation of free fatty acids in response to hunger, despite normalisation in carnitine levels in serum and a notable increase in excretion of carnitine esters in urine.

In conclusion, the identified studies and case study indicate ambiguous results concerning the efficacy of L-carnitine in MCADD therapy.

- carnitine uptake defect (CUD)

  In line with the results of the identified scientific evidence, L-carnitine supplementation in patients with carnitine uptake defect indicates efficacy in increasing free and total carnitine levels in serum (surrogate endpoint). It allows to completely eliminate symptoms (cardiomyopathy, hepatopathy) and prevent heart complications, but also to increase the ability to oxidise fatty acids in the skeletal muscles during physical effort and in other situations with the need for increased fatty acid oxidation, such as mental effort, stress, cold, chills, fever and fasting.

  In conclusion, the identified study,case studies and cases series indicate the results in favour of the gointervention in CUD therapy.

- multiple acyl-CoA dehydrogenation deficiency (MADD)

  L-carnitine supplementation in the population of MADD patients resulted in the improvement of psychomotor development in children (Rosa 2012, Yamaguchi 1991, Fontaine 1996), relief of abnormal neurological symptoms, return of liver function and size to normal (Mandel 1988), increase in muscle strength and pain relief (Macchione 2018, Pietrini 2014, Angelini 2014), normalisation of creatine kinase levels and no recurrence of rhabdomyolysis (Izumi 2011). Creanza 2017 described a case of a pregnant patient with MCADD, in whom dietary management, L carnitine and riboflavin supplementation enabled the proper course of pregnancy and giving birth to a healthy child.

  In conclusion, results of the identified case studies and case series are in favour of the intervention in treatment of MADD, however they are poor-quality evidence in the hierarchy of scientific reports.

Safety

No adverse effects related to L-carnitine treatment have been reported in the majority of the identified publications. In the studies which presented information on the safety of L-carnitine, the main adverse effects associated with treatment are hyperglycaemia (Berry 1988), and hepatic impairment has been observed in some patients (Hoffmann 1996). Furthermore, the main reported adverse effects were weight gain, intestinal disorders and bad body odour (Rasmussen 2014, Thomsen 2014)

The available publications indicated that the recorded deaths were caused by numerous complications. There is no information explaining to what extent these conditions were related to the application of L-carnitine and to what extent they were related with the patient's general condition and the other (than L-carnitine) applied treatment.

Additional safety information

No information on the safety of use of L-carnitine for healthcare professionals has been identified on the websites of pharmacovigilance organisations (i.a. the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products – URPL; the European Medicines Agency – EMA).

According to the information in the leaflet for Carnitor (containing lecarnitine), authorised by the FDA, very common and common adverse effects were not observed. Severe hypersensitivity reactions

including rash, urticaria and facial swelling were reported, mainly in patients with end-stage renal failure undergoing dialysis. The adverse effects included diarrhoea, nausea and vomiting. Their frequency has not been determined. Mild myasthenia was observed in only a few patients. Convulsions in patients with or without previous paroxysmal activity were reported.

According to the information provided by the Applicant, the website of the *WHO Uppsala Monitoring Centre* (an international database of adverse drug reaction reports) has identified a list of adverse effects reported during the use of Levocarnitine, which includes the number of recorded adverse effects between 1988 and 2019. The most frequently reported adverse effects were: general disorders and administration site conditions as well as stomach and intestinal disorders.

Limitations of the analysis

The following aspects impact the reliability of the clinical analysis:

- no RCTs on the use of L-carnitine in the population in question have been found. Therefore, the assessment of efficacy and safety of L-carnitine in the analysed indications was based on scientific evidence characterised by the lowest reliability: case studies, case series and non-randomised single-arm studies, and the possibility to generalise conclusions drawn on their basis is limited;
- in the identified studies, L-carnitine was used in therapy in combination with other products, so it is difficult to conclude that the results were solely due to L-carnitine supplementation;
- some publications do not provide information about the length of L-carnitine treatment, which constitutes important information in the context of the evaluation of results, as well as the characteristics of the indications in question requiring continuous supply of the product;
- in most studies, data on the safety of L-carnitine are either non-existent or rudimentary, which makes assessing the safety of the therapy impossible;
- The label of the L-carnitine product manufactured by Nutricia, in the section “Preparation and use” indicates that “the powder can be mixed with protein substitutes, added to single-ingredient foods, added to other foods and drinks authorised for consumption, dissolved in water or consumed as a paste”, which suggests oral administration. However, in its clinical analysis, the applicant included studies in which L-carnitine was administered both orally and by injection. It should be noted, however, that the agreed-upon drug programme does not specify the method of L-carnitine administration, while the efficacy of the therapy may depend on the route of administration.

The uncertainty of the clinical analysis results is affected by the following limitations:

- in some studies included in the analysis, no information has been provided as to whether the L-carnitine was administered to patients in a pure crystalline form.

Proposals of risk-sharing schemes

No risk-sharing scheme was proposed.

Economic analysis, including a cost-effectiveness estimation

An economic analysis consists in estimating and comparing the costs and health effects which may be associated with the use of a new therapy in an individual patient instead of therapies which are currently reimbursed.

The costs of the therapy are estimated in the Polish currency and the health effects are usually expressed using the life years gained (LYG) or the quality-adjusted life year (QALY) as a result of the therapy.

The comparison of values concerning the costs and effects related to the use of a new therapy and comparing them to the costs and effects of currently reimbursed therapies allow for obtaining an answer to the question on whether the health effect achieved as a result of the new therapy is associated with higher costs in comparison to the currently reimbursed therapies.

The achieved cost-effectiveness ratios are compared with the so-called cost-effectiveness threshold, i.e. which indicates that taking into account the means at the disposal of Poland (expressed in its GDP), the maximum cost of a new therapy necessary to obtain a unit of health effect (1 LYG or 1 QALY), compared to the currently available treatments, should not exceed three times the amount of per capita GDP.

Currently the cost-effectiveness threshold in Poland amounts to PLN 147,024 (3 x PLN 49,008).

The cost-effectiveness ratio does not estimate or determine the value of life, it only allows to assess and, among other things, select, a therapy associated with the potentially best use of the currently available resources.

The applicant carried out an economic analysis using a cost-minimisation analisis (CMA), comparing the L-carnitine reimbursed under the proposed drug programme with L-carnitine financed under the targeted import procedure.

The estimates include the public payer's perspective (the National Health Fund) and the common perspective (the NHF and the patient), which is identical to the payer's perspective due to the proposed reimbursement terms (drug programme, drug available to the patient free of charge).

The analysis was conducted in a one-year time horizon.

The following direct costs were included in the analysis:

- the cost of L-carnitine on the proposed reimbursement terms under the drug programme;
- the cost of L-carnitine under the targeted import procedure;
- the cost of monitoring a patient using L-carnitine imported under the targeted import procedure;
- the costs of qualification for treatment in the drug programme and monitoring its effectiveness;
- the costs of diagnosis under the drug programme in question.

However, the costs of drug administration were not included due to the lack of data on the percentage of patients receiving L-carnitine during hospitalisation or outpatient care.

According to the applicant's estimates, the annual total cost of using L-carnitine *[information protected as a trade secret]* under the targeted import procedure, the annual total cost amounts to PLN 22.3 thousand. Introduction of the proposed drug programme would reduce annual expenditure on treatment per patient *[information protected as a trade secret].*

The applicant carried out a deterministic sensitivity analysis, testing the effect of L-carnitine consumption on the patient (+/- 20%). The results of the sensitivity analysis are consistent with those of the basic analysis – *[information protected as a trade secret].*

Limitations of the analysis

In view of the available data, selecting CMA as the analytic technique should be deemed justified.

The estimation of annual consumption of L-carnitine per patient is based on the data of the Ministry of Health concerning the targeted import procedure. In the case of clinical indications not included in the data of the Ministry of Health, the average consumption based on the data of the Ministry of Health for other indications and based on the ratio of recommended doses was adopted. However, it should be noted that due to the uncertainty of these parameters, alternative assumptions for the average number of L-carnitine packages per patient were tested in the sensitivity analysis.

However, the sensitivity analysis did not test other parameters, such as the impact of alternative values of costs of inclusion in the programme, diagnostics or monitoring of treatment efficiency, which to some extent limits the possibility to draw conclusions from the presented analysis.

The cost of drug administration was not included in the analysis, which was justified by the lack of necessary data. Non-inclusion of the costs of drug administration can be viewed as a limitation of this analysis.

Indication whether the circumstances referred to in Article 13, paragraph 3 of the Act of 12 May 2011 on the reimbursement of drugs, foodstuffs for particular nutritional uses and medical devices (Journal of Laws No. 2019, item. 784)

In case the applicant's clinical analysis does not include randomised clinical trials which prove the superiority of the drug over the medical technologies which are currently reimbursed in the particular indication, it is the ex-factory price of the drug which must be calculated in such a way that the cost of using the drug applying for reimbursement is not higher than the cost of the health technology with the most favourable ratio of health effects to the cost of obtaining them.

It should be underlined that due to the lack of currently reimbursed health technologies in the indications in question, it is not possible to estimate the official selling price of the drug under Article 13 of the Act on reimbursement.

Analysis of the effects on the healthcare system, including budget impact analyses (BIA)

The analysis of the effects on the healthcare system consists of two important parts.

Firstly, the analysis of the impact on the payer's budget allows for estimating potential expenditure related to the financing of a new therapy from public funds.

The estimated expenditure related to the new therapy (the "tomorrow" scenario) is compared with how much currently is spent on the treatment of a particular health problem (the "today" scenario). On that basis it is possible to assess whether the new therapy will require a higher level of funding for the treatment of a particular health problem or whether it will involve savings in the payer's budget.

The budget impact assessment makes it possible to determine whether the payer possesses the necessary resources to finance a particular technology.

The second part of the analysis of the effects on the healthcare system raises the question on how the decision to finance a new therapy can affect the organisation of the provision of services (especially in the context of adjustments necessary for the new therapy to be used) and the availability of other healthcare services.

The analysis of the impact of a positive reimbursement decision on the healthcare system budget regarding L-carnitine in the drug programme in question was carried out in comparison with L-carnitine imported under the targeted import procedure.

The analysis was carried out from the perspective of the NHF. Given the lack of patients' co-payment for the health technology in question, the common perspective (the NHF and the patient) is identical to the public payer's perspective.

The estimations were carried out in a 2-year time horizon.

The costs were included in the analysis in a similar way as in the economic analysis.

The total number of patients eligible for the technology was estimated at *[information protected as a trade secret].*

Results of the budget impact analysis indicate that if a positive reimbursement decision is made to replace importing L-carnitine under the targeted import procedure with introduction of the drug programme, the estimated savings amount to *[information protected as a trade secret]* per year.

The applicant's sensitivity analysis analysed the impact on the results of the change in L-carnitine consumption per patient (+/- 20%) and the alternative size of the target population.

In the maximum variant (consumption of L-carnitine packages greater by 20%), the estimated *[information protected as a trade secret]* per year. Considering consumption of L-carnitine packages *lower by 20% [information protected as a trade secret].*

In the minimum variant (reduced target population), the estimated *[information protected as a trade secret]* per year.

Limitations of the analysis

The uncertainty of drawing conclusions based on the budget impact analysis depends i.a. on the following aspects.

The presented savings result from a reduction in the cost of L-carnitine; however, it should be noted that the costs related to qualification of patients to the drug programme and monitoring of its effectiveness should be expected to increase.

Furthermore, it should be underlined that the estimates of the target population size are based on *[information protected as a trade secret]***.**

The limitation of the analysis is also an issue related to the difficulty of precise dosage estimation, resulting from the fact that the dosage of L-carnitine should be strictly adjusted to the specific patient (the maximum possible dose ranges from 0 to 200 mg/kg body weight/day). Data on the number of L-carnitine packages imported under the targeted import procedure (data made available by the Ministry of Health for the purpose of the AOTMiT studies) were adopted in the analysis. In the case of clinical indications for which no data from the Ministry of Health were available, an arithmetic mean was adopted on the basis of the data de available by the Ministry of Health. The alternative assumptions concerning the average number of L-carnitine packages per patient were tested as part of the sensitivity analysis – the calculations indicated that the conclusions from the basic analysis were robust.

In its analysis, the applicant did not include the costs of drug administration. It is assumed that the administration or dispensing of L-carnitine may take place during hospitalisation or an outpatient care appointment. However, given that this is an undifferentiated cost, this does not affect the assumptions made in the model.

Remarks on the proposed risk-sharing instrument

Not applicable.

Remarks on the drug programme records

It is worth noting that no disease unit called “multiple acyl-CoA dehydrogenase deficiency” was found within the framework of the Agency's work. According to www.orpha.net, the abbreviation MADD is translated as “mulatiple acyl-CoA dehydrogenation deficiency” (other translations have also been identified in literature: “MAD deficiency” and “Glutaric acidemia type 2”). Thus, using the name of the disease unit in the drug programme according to the nomenclature used at www.orpha.net is recommended.

Review of the solutions proposed in the rationalisation analysis

The objective of the rationalisation analysis is to identify a mechanism which, if introduced, will result in a release of public funds in an amount at least corresponding to the increase in costs resulting from a positive decision to reimburse the intervention in question.

A rationalisation analysis is submitted if the budget impact analysis of the public payer demonstrated that the cost of reimbursement would increase.

[information protected as a trade secret]

Review of recommendations issued in other countries in relation to the technology in question

The following clinical guidelines were found during the search:

- British Inherited Metabolic Disease Group BIMDG 2018, 2015, 2008 (2017 update), 2008 (2016 update), 2008a (2016 update) (United Kingdom);
- National Health Service NHS 2018, 2016 (United Kingdom);
- Alberta Health Service AHS 2018 (Canada);
- European registry and network for Intoxication type Metabolic Diseases EIMD 2016 (Europe);
- N. Boy 2016;
- Yamada 2018.

It should be noted that the analysis of clinical recommendations includes documents published in the last 5 years.

In conclusion, the identified guidelines recommend carnitine supplementation as one of the components of treatment strategies. Doubts about the use of carnitine were raised only in the case of its use in the treatment of MCADD,(NHS 2016), as studies on its beneficial effect and tolerance are contradictory. However, the Yamada 2018 publication presents the limitations on the use of carnitine in LCHADD and VLCADD, because the beneficial effect of L-carnitine supplementation has not been proven.

For two indications (MCC and CUD), no guidelines published in the last 5 years have been found.

Furthermore, a summary of clinical recommendations presented within the framework of AOTMiT's previous studies concerning the use of L-carnitine in the indications in question was presented. The clinical guidelines identified at that time mention L-carnitine as a dietary component in the analysed indications:

3-Methylcrotonylglycinuria (MCC)

The search identified one recommendation (American Delphi-based consensus 2008) in which an expert panel recommends L-carnitine supplementation in both newborns/children with MCC and their mothers, if a reduced free carnitine level is found in their blood. L-carnitine supplementation is also recommended in children with symptoms of the disease and their mothers, regardless of the free carnitine level in the blood, due to the susceptibility to the deficiency of this substance in children with MCC. The recommendation indicates that such supplementation in some of the cases described in the literature has increased acyl-carnitine excretion but has not resulted in clinical improvement apart from compensating for carnitine deficiency.

Glutaric acidemia type 1

Four recommendations have been found (N. Boy 2016, BIMDG 2013, Kölker 2011 and EIMD 2011) – all of them emphasise the necessity of continuous L-carnitine supplementation in doses ensuring correct free L-carnitine serum levels (50-300 mg/kg body weight per day). In addition, the need to use a lysine-free diet and the administration of a protein equivalent in the form of lysine-free products should also be kept in mind. During acute episodes, the carnitine dose should be increased. The 2011 Kölker publication also describes the need to reduce tryptophan content in food.

Isovaleric acidemia

One recommendation has been found (BIMDG 2008a); it emphasised the necessity of glycine and L-carnitine administration. It is recommended that glycine be administered in 4 doses – the daily dose should amount to 300 mg/kg, while L-carnitine should be administered in a daily dose of 100 mg/kg.

Methylmalonic acidemia

Two recommendations were found (Baumagartner 2014, BIMDG 2008b), which underlined the need for a high calorie diet to prevent catabolism of endogenous proteins. At the same time, it is emphasised that the diet should contain limited amounts of amino acids: isoleucine, threonine, methionine and valine. In addition, administration of vitamin B12 (hydroxycobalamin) and antibiotics, such as neomycin and metronidazole, is recommended to reduce the production of propionic acid in the intestinal flora. L-carnitine supplementation is recommended at a dose of 50-300 mg/kg body weight per day, as high doses of L-carnitine administered orally play an important role in the removal of harmful organic metabolites.

Propionic acidemia

Four recommendations have been found (Baumgartner 2014, NIH 2012, Reid Sutton 2012 and BIMDG 2008c); they emphasise the need to stop or reduce protein intake. To prevent catabolism of endogenous proteins, fluids containing non-protein sources of calories should be administered intravenously. The need for L-carnitine supplementation is underlines. Furthermore, Baumgartner 2014 recommends oral supplementation with L-isoleucine and administration of antibiotics such as metronidazole and vitamin B12. L-carnitine treatment is considered to be safe. It is also underlined that treatment using L-carnitine, hydroxycobalamin, sodium benzoate and oral biotin plays an important role from the onset of symptoms until full diagnosis. Biotin plays an important role in the metabolism of fatty acids and amino acids.

Carnitine-acylcarnitine translocase deficiency

Two recommendations have been found (IDPH 2012 and Spiekerkoetter 2009). According to the IDPH 2012 recommendation, L-carnitine supplementation may be used in the case of fatty acid oxidation disorders (including CACT, which is extremely rare), depending on the disease. On the other hand, according to the European recommendation concerning long-chain fatty acid oxidation disorders, such supplementation is controversial due to the lack of published scientific evidence confirming the benefits of its long-term use. The recommendation does not include a direct reference to CACT.

Reimbursement recommendations

As a result of the search, positive reimbursement recommendations of the French agency Haute Autorité de Santé (HAS) of 2005, 2013 and 2015 for the use of Levocarnil (L-carnitine, 100 mg/ml oral solution, injection solution 1 g/5 ml) were also identified in the indications: systemic primary carnitine deficiency and primary muscle carnitine deficiency, secondary carnitine deficiency related to organic acidemia and disorder of beta-oxidation of fatty acids. In the justification of the most recent HAS recommendation of 2015, it was indicated that carnitine deficiency is a serious health problem that may affect the survival of patients. The assessed product is part of substitution therapy. Levocarnil constitutes first-line treatment to which there are no alternative options.

In addition, as a result of a previous search concerning the assessment of L-carnitine as regards the appropriateness of issuing an approval for reimbursement under the targeted import procedure, an information from 2017 issued by the *Pharmaceutical Management Agency* (PHARMAC), concerning approvals to reimburse L-carnitine for individual patients in New Zealand in the treatment of metabolic diseases during the period 1 March 2012-31 August 2017, has been found, as well as the information that the *Ontario Ministry of Health* (OMH) in Canada reimburses L-carnitine under the *Inherited Metabolic Diseases* programme in organic acidemias, fatty acid oxidation disorders, carnitine uptake deficiency and secondary carnitine deficiency.

The current list of drugs financed under the The Exceptional Access Program (EAP) in Canada of December 2019 includes the following forms of L-carnitine for oral use: Carnitor 100 mg/ml oral solution, Carnitor 330 mg tablets and Carnitor 200 mg/ml injection.

In line with information presented by the applicant, L-carnitine is financed in 3 EU and EFTA states (of the 31 indicated). The level of reimbursement from public funds usually amounts to 100% and no risk-sharing instruments are used.

Legal basis for the recommendation

The recommendation was prepared on the basis of an order of the Minister of Health of 16/01/2020 (reference number: PLR.4600.1416.2019.10.PB (JKB)), with regard to preparation of the recommendation of the President of the AOTMiT on whether the following foodstuff for particular nutritional use should be reimbursed: L-carnitine, powder, 50 x 1 g. EAN: 5016533045017, in the following indications: under the following drug programme: "Adjuvant therapy using L-carnitine in the following indications: 3-Methylcrotonylglycinuria – MCC, glutaric acidemia type 1 – GA I, isovaleric acidemia – IVA, methylmalonic acidemia – MMA, propionic acidemia – PA, long-chain fatty-acid oxidation disorders – LC-FAOD, medium-chain acyl-CoA dehydrogenase deficiency – MCADD, carnitine uptake defect – CUD, multiple acyl-CoA dehydrogenation deficiency – MADD (E 71.1, E 71.3, E 72.3)", pursuant to Article 35 paragraph 1 of the Act of 12 May 2011 on the reimbursement of drugs, foodstuffs for special nutritional purposes and medical devices (Journal of Laws of 2019, item 784, as amended), upon the receipt of the Position of the Transparency Council No. 17/2020 of 10 February on the evaluation of the following foodstuff for particular nutritional use: L-carnitine; under the following drug programme "Adjuvant therapy using L-carnitine in the following indications: 3-Methylcrotonylglycinuria – 3-MCC, glutaric acidemia type 1 – GA I, isovaleric acidemia – IVA, methylmalonic acidemia – MMA, propionic acidemia – PA, long-chain fatty-acid oxidation disorders – LC-FAOD, medium-chain acyl-CoA dehydrogenase deficiency – MCADD, carnitine uptake defect – CUD, multiple acyl-CoA dehydrogenation deficiency – MADD (E 71.1, E 71.3, E 72.3)".

References

1. Position of the Transparency Council 17/2020 of 10 February 2020 on the assessment of the following foodstuff for particular nutritional use: L-carnitine; under the following drug programme "Adjuvant therapy using L-carnitine in the following indications: 3-Methylcrotonylglycinuria – 3-MCC, glutaric acidemia type 1 – GA I, isovaleric acidemia – IVA, methylmalonic acidemia – MMA, propionic acidemia – PA, long-chain fatty-acid oxidation disorders – LC-FAOD, medium-chain acyl-CoA dehydrogenase deficiency – MCADD, carnitine uptake defect – CUD, multiple acyl-CoA dehydrogenation deficiency – MADD (E 71.1, E 71.3, E 72.3)".
2. Application for the reimbursement of L-carnitine under the following drug programme "Adjuvant therapy using L-carnitine in the following indications: 3-Methylcrotonylglycinuria – MCC, glutaric acidemia type 1 – GA I, isovaleric acidemia – IVA, methylmalonic acidemia – MMA, propionic acidemia – PA, long-chain fatty-acid oxidation disorders – LC-FAOD, medium-chain acyl-CoA dehydrogenase deficiency – MCADD, carnitine uptake defect – CUD, multiple acyl-CoA dehydrogenation deficiency – MADD (E 71.1, E 71.3, E 72.3)". Verification analysis No. OT.4331.2.2020; completion date: 03/02/2020