EU Risk Management Plan for Maapliv

Active substance(s) (INN or common name):	Amino acids solution (n=16) L-alanine, L-arginine, L-aspartic acid, L-cysteine hydrochloride monohydrate (equivalent to L-Cysteine), L-glutamic acid, Glycine, L-histidine, L-lysine monohydrate (equivalent to L-Lysine), L-methionine, L-phenylalanine, L-proline, L-serine, Taurine, L-threonine, L-tryptophan, L-tyrosine.
Pharmacotherapeutic group (ATC Code):	Amino acids for parenteral use ATC code: B05BA01
Name of Marketing Authorisation Holder or Applicant:	Recordati Rare Diseases Tour Hekla 52 avenue du Général De Gaulle 92800 Puteaux France
Number of medicinal products to which this RMP refers:	1
Product concerned (brand name):	Maapliv

Version Number: 1.3
Date of final sign-off: 15 May 2025

Rationale for submitting an RMP.

Maapliv is a Branched-Chain Amino Acid (BCAA) free solution for parenteral use indicated for the treatment of Maple Syrup Urine Disease (MSUD) presenting with an acute decompensation episode in patients from birth who are not eligible for an oral or enteral BCAA-free formulation.

In accordance with Regulation (EC) N°141/2000 of 16 December 1999, the Committee for Orphan Medicinal Products (COMP) adopted a positive opinion on 13 September 2018 recommending the granting of an orphan designation.

This initial Risk Management Plan (RMP) is submitted as part of the first Marketing Authorisation Application for Maapliv via the centralized procedure, under the status of Well-Established Medicinal Use (WEU) according to Article 10a of Directive 2001/83/EC and to part II1 of Annex I to Directive 2003/63/EC.

The document is compiled for regulatory authorities in a format proposed by ICH E2E and according to the Guideline on good pharmacovigilance practices (GVP, Module V – Risk management systems [Rev 2]). It summarizes the risk management system, which is a set of pharmacovigilance activities and interventions designed to identify, characterize, prevent, or minimize risk, including the assessment of the effectiveness of those interventions.

Part	Module/annex
Part I Product overview	None
Part II Safety Specification	SI Epidemiology of the indication and target population(s)
	SII Non-clinical part of the safety specification
	SIII Clinical trial exposure
	SIV Populations not studied in clinical trials
	SV Post-authorisation experience
	SVI Additional EU requirements for the safety specification
	SVII Identified and potential risks
	SVIII Summary of the safety concerns
Part III Pharmacovigilance Plan	
Part IV Plan for post-authorisation efficacy studies	
Part V Risk Minimisation Measures	
Part VI Summary of RMP	
Part VII Annexes	Annex 1 Eudravigilance interface
	Annex 2 Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme
	Annex 3 Protocols for proposed, ongoing, and completed studies in the pharmacovigilance plan
	Annex 4 Specific adverse drug reaction follow-up forms
	Annex 5 Protocols for proposed and on-going studies in RMP part IV
	Annex 6 Details of proposed additional risk minimisation activities (if applicable)
	Annex 7 Other supporting data (including referenced material)
	Annex 8 Summary of changes to the risk management plan over time

OTHER RMP VERSIONS UNDER EVALUATION

Not applicable.

DETAILS OF THE CURRENTLY APPROVED RMP

Not applicable

CONTACT PERSON AND EU QPPV

Name and contact details of the QPPV:
Mrs. Anne Valot-Salengro, MD

QPPV Signature: *electronic signature*

DocuSigned by:
Anne VALOT SALENGRO
FDB90D57ECD8490...

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

AA	Amino Acid
ADR	Adverse Drug Reaction
BCAA	Branched-Chain Amino Acid
BCKDH	Branched Chain α-Ketoacid Dehydrogenase
COMP	Committee for Orphan Medicinal Products
CVC	Central Venous Catheter
GVP	Guideline on Good Pharmacovigilance Practices
IV	Intravenous
MSUD	Maple Syrup Urine Disease
PDH	Pyruvate Dehydrogenase
PE	Pulmonary Embolism
PN	Parenteral Nutrition
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TPN	Total Parenteral Nutrition
WEU	Well-Established Medicinal Use
αKGDH	α-KetoGlutarate DeHydrogenase

1. PART I: PRODUCT(S) OVERVIEW

Invented name(s) in the European Economic Area (EEA)	Maapliv
Active substance(s) (INN or common name)	Amino acids solution (n=16) L-alanine, L-arginine, L-aspartic acid, L-cysteine hydrochloride monohydrate (equivalent to L-Cysteine), L-glutamic acid, Glycine, L-histidine, L-lysine monohydrate (equivalent to L-Lysine), L-methionine, L-phenylalanine, L-proline, L-serine, Taurine, L-threonine, L-tryptophan, L-tyrosine.
Pharmacotherapeutic group(s) (ATC Code)	Amino acids for parenteral use ATC code: B05BA01
Marketing Authorisation Holders	Recordati Rare Diseases
Medicinal products to which this RMP refers	1
Marketing authorisation procedure	Centralised
Brief description of the product	The BCAA-free amino-acid solution promotes protein anabolism and hence reduces toxic levels of BCAAs and their corresponding keto-acids, thereby preventing cerebral oedema, metabolic imbalances, neurotransmitter deficiencies, and mitochondrial alterations.
Hyperlink to the Product Information	See Module 1, Section 1.3.1 - SPC, Labelling and Package Leaflet
Indication(s) in the EEA	Current: None Proposed: Maapliv is indicated for the treatment of maple syrup urine disease (MSUD) presenting with an acute decompensation episode in patients from birth who are not eligible for an oral and enteral branched-chain amino acids free (BCAA- free) formulation.
Dosage in the EEA	The posology of Maapliv may be adapted according to several factors, including the patient's age, weight, and clinical condition. A 24-hour infusion is recommended.

	The treatment may be maintained until the resolution of decompensation episodes (leucine plasma level below 381 µmol/L). In adults, adolescents, and children, a dose of 1 to 2 g/kg/day, corresponding to a volume of 19 to 39mL per kg and per day (0.79 to 1.6mL/kg/per hour), should be administered. In new-born and infants up to 2 years old, a dose of 2 to 3 g per kg and per day, corresponding to 38 to 58 mL per kg and per day (1.6 to 2.4 mL/kg/hour) should be administered. The product should be administered by continuous central or peripheral intravenous infusion.
Pharmaceutical form(s) and strengths	Solution for infusion 26.375g per 500 mL
Is/will the product be subject to additional monitoring in the EU?	No

2. PART II: SAFETY SPECIFICATION

2.1. PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

Maple Syrup Urine Disease is an inborn error of amino acid (AA) metabolism caused by a deficiency of the mitochondrial enzyme branched-chain α-ketoacid dehydrogenase (BCKDH complex activity, resulting in the accumulation of the branched-chain amino acids (BCAAs), leucine, isoleucine, and valine as well as their metabolites (i.e., α-ketoacids). Branched-chain amino acids (BCAAs) and metabolites that rise in plasma concentrations may result in severe complications. Episodes of metabolic decompensation are acute medical emergencies and may occur at any time or any age after trauma, surgery, illness, or inappropriate dietary intake. Failure to lower leucine levels in a timely manner may result in permanent morbid sequelae, including disability and death, since acute metabolic decompensation may be fatal. If not appropriately diagnosed and treated, rapid elevation of circulating leucine and its ketoacid, α-ketoisocaproate, can cause encephalopathy and life-threatening brain swelling. This can lead to irreversible neurological complications, including, metabolic decompensation and death (Strauss KA et al., 2010). Besides overt acute toxicity, children with the disease often experience subacute consequences. Many MSUD children exhibit subtle neurologic dysfunction, such as attention-deficit disorder or learning disabilities. This is true even for children who have been identified prospectively and who appear to be well-controlled, making it difficult to explain these observations. One of the sources of variation may be the degree of a metabolic block of the branched-chain α-ketoacid dehydrogenase complex (Brosnan JT, 2005).

Once the children have passed the critical period, they need a permanent reduction in their dietary intake of BCAAs to maintain plasma levels close to normal. The amount of natural protein is thus highly restricted, and large amounts of protein substitutes in the form of BCAAs-free amino acid mixtures are necessary. Regular, close monitoring of blood BCAA levels is essential to titrate their intake to maintain target plasma concentrations. Discontinuation of the diet as well as febrile illnesses resulting in an increase in catabolism and amino acid release from muscle protein can precipitate severe metabolic decompensation at any age, leading to acute encephalopathy that requires emergency treatment (Simon E et al., 2005).

There are different forms of MSUD:

Classic MSUD is the most severe form of the disease, as it corresponds to the lowest percentage of normal BCKDH activity (0% to 2%). Soon after birth, maple syrup odour is evident in the cerumen and then in the urine. Infants develop serious symptoms within 48 hours of delivery when rising blood levels of leucine and its corresponding metabolites surpass critical concentrations and initiate neurotoxic effects. When MSUD is first suspected, which is usually the case after 10 days of life, plasma leucine concentrations range between 2.5 and 4-5 mmol/L (normal: <150 µmol/L). There is evidence that in patients with classic MSUD, neurodevelopmental outcomes are 1) inversely related to the duration of high plasma leucine levels during the neonatal illness and 2) inversely related to the longitudinal plasma leucine

concentrations in childhood, which is an indicator of the quality and compliance of dietary treatment (Simon E et al., 2005). In the following few days, symptoms include feeding difficulties, lethargy, stereotyped movements, autonomic dysregulation, bradycardia, hypothermia, and axial hypotonia with episodes of distal hypertonia that could lead to cerebral oedema, coma, and central respiratory failure (Morton DH et al., 2002; Strauss KA et al., 2010; Knerr I et al., 2012; Villani GR et al., 2017).

Intermediate MSUD is a less severe form of the disease, and the onset is variable, typically between the ages of 5 months and 7 years. BCKDH activity ranges between 3 and 30% of normal. Beyond the classic MSUD symptoms, patients suffer developmental delays and mental retardation (Strauss KA et al., 2010; Villani GR et al., 2017).

Intermittent MSUD age onset is variable, the BCKDH activity ranges between 5 and 20% of normal, and patients have normal early growth and development, but they can experience episodic decompensation episodes (Strauss KA et al., 2010; Villani GR et al., 2017).

Thiamine-responsive MSUD has a similar clinical course to intermediate MSUD (Villani GR et al., 2017).

The dihydrolipoamide dehydrogenase deficiency, also known as MSUD type III is caused by the deficiency of the E3 subunit of BCKDH, α-ketoglutarate dehydrogenase (αKGDH), and pyruvate dehydrogenase (PDH) (Quinonez SC et al., 2014). The most frequent is the severe form, characterized by metabolic acidosis, encephalopathy, feeding difficulties, liver failure, and early death (Blackburn PR et al., 2017).

2.1.1. SI.1 Indication

Maapliv is indicated for the treatment of MSUD presenting with an acute decompensation episode in patients from birth who are not eligible for an oral and enteral branched-chain amino acids free (BCAA- free) formulation.

2.1.2. SI.2 Epidemiology of the disease

Incidence and prevalence

The global estimated prevalence of MSUD according to Orphanet reports is 1 to 9 for one million, corresponding to an approximate total number of patients between 500 and 5,000. The global MSUD incidence estimate (classical and occasionally intermediate) is 1 in 185,000 live births (0.54/100,000) (Goyanes A et al., 2019). In Europe, the incidence of MSUD is approximately 0.5/100,000 births, yielding approximately 26 new cases per year (Orphanet 2018). MSUD prevalence is higher in some populations such as Galician in Spain (1/52,541) (Couce ML et al., 2011), and Ashkenazi Jewish in the United States (1/26,000 live births) (NORD, Rare disease database).

Data on the incidence of decompensation episodes are lacking. It can be assumed that patients with MSUD will experience several metabolic decompensation episodes throughout their lives.

2.1.3. SI.3 Current therapies for MSUD

The treatment of classic, intermediate, intermittent, and thiamine-responsive MSUD has three chief components: 1. Lifelong therapy to maintain an acceptable diet; 2. Life-long maintenance of normal metabolic conditions, including the levels of BCAAs in the body; 3. immediate medical intervention for metabolic crises.

Protein restriction must start as soon as possible after birth to promote proper growth and development (Strauss KA et al., 2010; Strauss KA et al., 2020). Artificially made (synthetic) formulas for oral/enteral administration are available that provide all the nutrients necessary for proper growth and development but lack leucine, isoleucine, and valine (Abbott Ketonex® MSUD, MSUD Anamix® Infant, MSUD Maxamid®, MSUD Express®, MSUD Maxamum® Nutricia, MilupaTM MSUD 2). These three amino acids are essential nutrients that are added to the diet separately in small amounts depending on their plasma levels and residual enzyme activity. The oral/enteral treatment with BCAA-free mixtures associated with a high caloric diet and adequate amino acid supplementation was shown to normalise leucine plasma levels while enhancing protein synthesis.

Even if affected individuals follow the specialized diet strictly, the risk of metabolic crisis always remains. The aim of therapy for metabolic crises is to try and reduce and then reverse the increased protein catabolism that is the root cause of such episodes. Episodes of metabolic crisis require immediate medical intervention to lower the levels of branched-chain amino acids, especially leucine, in the blood. The oral/enteral treatment with BCAA-free mixtures associated with a high caloric diet and adequate amino acid supplementation was shown to normalise leucine plasma levels while enhancing protein synthesis. Various extracorporeal techniques have been used to reduce plasma leucine levels, including dialysis (haemodialysis, peritoneal dialysis) or a process in which blood is removed from the body and passed through a filter before being returned to the body (hemofiltration), in patients with the most critical decompensation episodes.

A pivotal component of the therapy is the use of BCAA-free mixtures. Currently commercialised mixtures are used as food supplements for long-term dietary maintenance and are not specifically designed for the treatment of decompensation episodes.

Their administration is limited to the enteral route, either by oral feeding, nasogastric intubation, or gastrostomy. In the context of metabolic decompensations, which require urgent BCAA-free administration, the enteral route is inappropriate for patients presenting clinical symptoms such as coma, seizures, gastric intolerance, nausea, and vomiting, or for patients refusing nasogastric tubing (frequent for adolescents), and it is not appropriate as a preventive treatment before planned surgery (Abi-Warde MT et al., 2017; de Lonlay P et al., 2021; Alili JM et al., 2022). The intravenous (IV) administration of a BCAA-free mixture in all these circumstances is an essential alternative, potentially avoiding invasive or aggressive interventions such as gastrostomy, which is especially relevant for the younger, vulnerable target population (Servais A et al., 2013; Frazier DM et al., 2014; Abi-Warde MT et al., 2017; Alili JM et al., 2022; Sanchez-Pintos P et al., 2022).

In April 2021, a guideline for the management of the disease recommending the use of parenteral BCAA-free formulations was published by French Health Authorities: The French National Protocol for the Diagnosis and Care of MSUD (Protocole National de Diagnostic et de Soins (PNDS) Leucinose. 2021).

No medicinal product containing a BCAA-free solution, nor a medicinal product for IV administration allowing a prompt medical intervention for the treatment of DEs in MSUD patients, was approved in Europe. In Europe, BCAA-free solutions intended for IV administration in MSUD patients had been prepared locally for years in hospital pharmacies and thus were not immediately accessible, and individual subject variability was questionable.

Liver transplantation has been used to treat individuals with classic MSUD. This procedure has resulted in individuals who are symptom-free and able to eat normal foods. The new liver supplies enough enzyme activity to breakdown the three BCAAs. However, the availability of a donor's liver and the high cost are hurdles to this procedure.

2.1.4. SI.4 Important co-morbidities found in the target population.

Maple Syrup Urine Disease is a genetic disorder that affects amino acid metabolism. Along with the primary symptoms related to the accumulation of branched-chain amino acids (leucine, isoleucine, and valine), individuals with MSUD may experience various co-morbidities (De Castro-Hamoy LG et al., 2017). Some of the commonly observed co-morbidities in MSUD patients are as follows:

Neurological impairment: MSUD can cause neurological problems, including developmental delays, intellectual disability, learning difficulties, and behavioural issues. Severe cases of MSUD can lead to encephalopathy, which may result in seizures, coma, and even death if left untreated.

Metabolic imbalances and crisis: The metabolic disruptions caused by MSUD can result in imbalances in other metabolites. For example, individuals with MSUD may have elevated levels of other amino acids, such as alanine, glutamine, and threonine. They may also experience disturbances in glucose metabolism and altered levels of organic acids (Xu J et al., 2020; MSUD 2020). Without proper management and adherence to dietary restrictions, individuals with MSUD are at risk of experiencing metabolic crises. These crises can be triggered by stressors such as infections, trauma, surgery, or dietary non-compliance. Metabolic crises can lead to severe neurological deterioration and life-threatening complications if not promptly treated.

Growth and nutritional issues: MSUD can affect growth and nutrition in affected individuals. Poor feeding, growth retardation, and failure to thrive are common problems observed in infants and young children with MSUD (MSUD, Children's Hospital of Philadelphia).

Psychiatric and behavioural disorders: Some individuals with MSUD may develop psychiatric and behavioural disorders, including anxiety, depression, attention deficit hyperactivity disorder (ADHD), and autistic-like behaviours. These conditions may require additional

support and management alongside MSUD treatment (Strauss KA et al., 2006). The incidence of attention-deficit/hyperactivity disorder in MSUD often exceeds 50%. In classic MSUD, the probability of developing a psychiatric comorbidity (depression, anxiety, etc) is between 83% and 100% by age 35 years.

2.2. PART II: MODULE SII – NON-CLINICAL PART OF THE SAFETY SPECIFICATION

2.2.1. SII.1 Introduction

Since 2010, AGEPS (Agence Générale des Equipements et Produits de Santé, France) has manufactured a BCAA-free solution for parenteral use containing essential L-amino acids (His, Lys, Met, Phe, Thr, Trp) and non-essential L-amino acids (Ala, Arg, Asp, Cys, Glu, Gly, Pro, Ser, Tyr) and taurine. This product has been used in France for the treatment of MSUD DEs in some studies. Recordati Rare Diseases (RRD) aimed to escalate and optimise to a "pharma" grade the manufacturing of the product to ensure reliability and reproducibility of the effects and to standardise its pharmaceutical quality. This process resulted in Maapliv, which corresponds qualitatively and quantitatively to the AGEPS product.

2.2.2. SII.2 Non-clinical data

No safety pharmacological studies and no toxicology studies were conducted with Maapliv. However, the data available from using Maapliv in the safe and effective treatment of MSUD, the long-term exposure of humans to the component amino acids of Maapliv through a normal diet, and nonclinical toxicity data for individual amino acids compensate for a lack of regulatory toxicology studies for Maapliv.

2.2.3. SII.3 Conclusion on non-clinical data

No toxic signal was reported in any study or from practice that would raise a safety concern with the administration of Maapliv.

2.3. PART II: MODULE SIII – CLINICAL TRIAL EXPOSURE

Maapliv is a solution for infusion devoid of leucine, isoleucine, and valine, containing 16 other amino acids. No clinical trials were conducted with Maapliv per se, but prospective/retrospective MSUD patient cohorts were studied in which patients were administered the AGEPS product. Therefore, all data reported herein are extracted from publications in which patients were exposed to the BCAA-free solution corresponding to Maapliv (Servais A et al., 2013; Blanco Dorado S, 2017; de Lonlay P et al., 2021; Alili JM et al., 2022; Sanchez-Pintos P et al., 2022).

In these publications, 30 patients followed up from the neonatal period up to the adult age received parenteral infusions of the BCAA-free solution corresponding to Maapliv for the treatment of 132 metabolic decompensation episodes.

In 4 supportive studies (Townsend I and Kerr DS, 1982; Berry GT et al., 1991; Morton DH et al., 2002; Couce Pico ML et al., 2007), 14 patients who experienced 26 decompensation episodes were exposed to a parenteral BCCA-free mixture other than Maapliv.

2.4. PART II: MODULE SIV – POPULATIONS NOT STUDIED IN CLINICAL TRIALS

2.4.1. SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

There were no pivotal clinical trials conducted with Maapliv. In the publication with the BCAA-free solution corresponding to Maapliv, no exclusion criteria were described.

2.4.2. SIV.2 Limitations to detect adverse reactions in clinical trial development programmes.

The size of the MSUD population studied may be too small to appropriately detect relevant adverse reactions and adequately describe the safety profile of Maapliv.

2.4.3. SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes.

A total of 30 patients with classical MSUD were enrolled in the patient cohorts.

- There was no patient included with other types of MSUD, meaning that patients diagnosed with intermediate MSUD, intermittent MSUD, thiamine responsive MSUD, and Type III MSUD have not been studied. However, these patients may experience episodic decompensation episodes as well, which are managed and treated likewise.
- There were no pregnant or breast-feeding women in the studies.
- Patients with relevant co-morbidities (hepatic impairment, renal impairment, cardiovascular impairment, and immunocompromised patients) were not included. In patients with severe hepatic impairment, it is known that the administration of amino acid solutions may result in plasma amino acid imbalance, hyperammonaemia, stupor, and coma, although this has not been described in the publications with the BCAA-free solution corresponding to Maapliv. In patients with impaired renal function, the administration of amino-acid solutions may increase an already elevated blood urea nitrogen, but this has never been reported in the publications with the BCAA-free solution corresponding to Maapliv. In patients with compromised cardiac function (heart failure, pulmonary oedema), the infusion of large volumes of amino acid solutions may also deteriorate the patient's status.
- Paediatric and adult patients were well represented as the detection of the disease frequently occurs shortly after birth, but elderly patients (≥ 65-year-old) were not represented. It is noteworthy that the elderly population is the one who may suffer more from hepatic, renal, and cardiac impairment.

2.5. PART II: MODULE SV – POST-AUTHORISATION EXPERIENCE

2.5.1. SV.1 Post-authorisation exposure

SV.1.1 Method used to calculate exposure.

Not applicable.

SV.1.2 Exposure

Not applicable.

2.5.2. SV.2 Use of the medicinal product

Not applicable.

2.6. PART II: MODULE SVI – ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Not applicable (There is no potential for misuse for illegal purposes).

2.7. PART II: MODULE SVII – IDENTIFIED AND POTENTIAL RISKS

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

Not applicable as this is the first RMP.

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP.

- Local reactions have not been reported in the published clinical trials with the BCAA-free solution corresponding to Maapliv. However, due to its rather low hypertonicity, (osmolality: 475 mOsmol/Kg), Maapliv can be infused by peripheral catheter and the MAH considers that hypertonic infusion solutions may cause irritation of the vein when administered into a peripheral vein. Local reactions are therefore possible but are not considered as important for inclusion in the list of safety concerns.
- Allergic reactions (other than anaphylaxis) are not considered as important to be included in the important potential risk. There was no such ADR reported in the published clinical trials with the BCAA-free solution corresponding to Maapliv. They are rare with amino-acid solutions and are generally reported as cutaneous manifestations such as a cutaneous rash, and erythema with or without pruritus. These reactions are generally mild in intensity, not serious, and do not impact the patient outcome (Vikram C, 2018). They have been notably described with AA solutions containing bisulphite, which is not the case with the BCAA-free solution corresponding to Maapliv.
- Azotaemia: is not considered as important to be included in the important potential risk. There was no such ADR reported in the published clinical trials with the BCAA-free solution corresponding to Maapliv. The plasma urea concentration is normally increased in proportion to the rate of protein provision, but it is well known that plasma urea

concentrations are far more greatly influenced by renal blood flow and renal functional mass than the rate of protein provision. The available evidence suggests that protein provision in doses between 2.5 and 3.0 g/kg normal weight per day is safe for use in clinical practice (Hoffer, 2017), as recommended in Maapliv Summary of Product Characteristics (SmPC).

- Anaphylactic reaction is not considered as important to be included in the important potential risk. According to the SmPC for Maapliv, frequency of anaphylactic reactions is listed as not known, and hypersensitivity reaction to Maapliv is adequately described as a contraindication for Maapliv. The information in the SmPC is considered sufficient and this risk is well managed with routine risk mitigation measures and additional risk minimization measures are not deemed necessary. Moreover, the available data do not suggest a significant risk beyond what is already managed through routine clinical practices. Hence, this risk does not meet criteria for inclusion in the RMP in alignment with GVP Module V, Rev 2.0.
- Cholestasis reaction is not considered as important to be included in the important potential risk. According to the SmPC for Maapliv, frequency of cholestasis is listed as not known. The information in the SmPC is considered sufficient and this risk is well managed with routine risk mitigation measures and additional risk minimization measures are not deemed necessary. Moreover, the available data do not suggest a significant risk beyond what is already managed through routine clinical practices. Hence, this risk does not meet criteria for inclusion in the RMP in alignment with GVP Module V, Rev 2.0.

- Hyperammonaemia is not considered as important to be included in the important potential risk. According to the SmPC for Maapliv, frequency of hyperammonaemia is listed as not known. Special warnings and precautions section of the SmPC adequately warrants that patients with hepatic impairment may result in hyperammonaemia. Liver function parameters should be closely monitored in these patients, and they should be monitored for possible symptoms of hyperammonaemia. This risk is well managed with routine risk mitigation measures; and additional risk minimization measures are not deemed necessary. Moreover, the available data do not suggest a significant risk beyond what is already managed through routine clinical practices. Hence, this risk does not meet criteria for inclusion in the RMP in alignment with GVP Module V, Rev 2.0.

- Thromboembolism is not considered as important to be included in the important potential risk. According to the SmPC for Maapliv, frequency of pulmonary vascular embolism is listed as not known. This risk is well managed with routine risk mitigation measures and additional risk minimization measures are not deemed necessary. Moreover, the available data do not suggest a significant risk beyond what is already managed through routine clinical practices. Hence, this risk does not meet criteria for inclusion in the RMP in alignment with GVP Module V, Rev 2.0.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP.

2.7.1. 1.1. Important identified risks

Not applicable since no ADR was reported in the published clinical trials with the BCAA-free solution corresponding to Maapliv.

2.7.1. 1.2. Important potential risks

Not applicable. As stated above, there was no report of ADRs with the parenteral use of the BCAA-free solution corresponding to Maapliv in the published results of clinical trials (de Lonlay P et al., 2021; Alili JM et al., 2022; Sanchez-Pintos P et al., 2022). The Applicant will continue monitoring the safety information via routine pharmacovigilance activities and a registry.

2.7.1. 1.3. Missing information

- Long term safety

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

SVII.2.1 Introduction

Not applicable.

SVII.2.2 Reclassification of the risks

Not applicable.

SVII.2.3 Conclusion

Not applicable.

2.7.3. 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

Not applicable since there are no important identified risks and potential risks included in this RMP for Maapliv.

SVII.3.2 Presentation of the missing information

The following missing information has been defined for the patient population for whom there are insufficient or limited data during the development phase.

Missing Information: Long term safety

Evidence source	The data on the safety during repeated use of MAAPLIV remains limited, as we do not have data on patients over repeated episodes treated with MAAPLIV therapy. Since MAAPLIV is indicated only for use during acute decompensation episodes of MSUD, a long-term safety monitoring of patients over multiple episodes rather than continuous treatment exposure would be required. Considering there are uncertainties due to intermittent use of the product rather than continues use and a limited disease population, the post-authorization registry study will further provide the evidence to assess its long-term safety profile, including potential risks associated with prolonged use.
Population in need of further characterisation	Due to the limited data, efficacy and safety data on the repeated use of MAAPLIV in the real-world setting needs to be further evaluated.

2.8. PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

A summary of the safety concerns identified in the previous modules of this RMP is provided in Table 1.

Table 1 - Summary of Safety Concerns

Important Identified Risks	• None
Important Potential Risks	• None
Missing Information	• Long-term safety

3. PART III: PHARMACOVIGILANCE PLAN

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities as described in the Recordati Pharmacovigilance System Master File will be conducted to identify any new safety concern associated with Maapliv. Safety data from the post-marketing environment will be continuously monitored and assessed to identify new safety concerns or characterize the risks associated with the product.

III.2 Additional pharmacovigilance activities

No additional pharmacovigilance activities are in place or proposed for MAAPLIV..

III.3 Summary table of additional pharmacovigilance activities

Not applicable

4. PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Table 2: Planned and Ongoing Post-authorization Efficacy Studies That Are Conditions of the Marketing Authorization or That Are Specific Obligations

Study/Status	Summary of Objectives	Efficacy Uncertainties Addressed	Milestones	Due Dates
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
A registry of patients with maple syrup urine disease (MSUD) treated with MAAPLIV	**Primary Objectives:** Characterize safety and efficacy outcomes on MAAPLIV during acute metabolic decompensation episodes. **Secondary objectives:**	Long term safety and efficacy Describe efficacy profile per MSUD subtype and per severity of the	Protocol submission Annual interim report	First quarter of 2026 Interim reports will be submitted upon

Study/Status	Summary of Objectives	Efficacy Uncertainties Addressed	Milestones	Due Dates
Planned	1. Describe the association between plasma leucine levels and clinical symptom resolution 2. Describe the characteristics of responders/non-responders patients per episode to MAAPLIV 3. Describe the acute decompensation episode outcomes per MSUD subtypes, or per disease severity (i.e. leucine level at baseline) 4. Describe therapeutic management of acute decompensation episodes: hospitalization (duration, unit), decompensation episode treatments (including emergency diet management, MAAPLIV and other concomitant treatments). 5. Evaluate real-world treatment healthcare resource utilization (HRU). 6. Measure the health-related quality of life outcomes for patients and caregivers.	decompensation episode based on leucine level at baseline		periodic annual re-assessment

5. PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

5.1. V.1 Routine risk minimization measures

Table 3: Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization Activities
Missing information	
Long term safety	Routine risk communication • SmPC 4.4 and section 2 of the PI mentions that there is limited information on the repeated administration of the intravenous

	BCAA-free formula Routine risk minimization activities recommending specific clinical measures to address the risk: None Other routine risk minimization measures beyond the Product Information: • Special medical prescription

5.2. V.2 Additional risk minimisation activities

There is no specific safety concerns associated with Maapliv. Therefore, no additional risk minimization measures are warranted beyond the standard pharmacovigilance activities such as adverse reaction reporting, Periodic Safety Reporting, and Signal Detection as described in the Recordati Pharmacovigilance System Master File.

5.3. V.3 Summary of risk minimisation measures

Table 4: Summary Table of Risk Minimization and Pharmacovigilance Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Missing information		
Long term safety	Routine risk minimization measures: • SmPC 4.4 and section 2 of the PI mentions that there is limited information on the repeated administration of the intravenous BCAA-free formula. Other routine risk minimization measures beyond the Product Information: • Special medical prescription Additional risk minimization measures: • No risk minimization measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None

6. PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Maapliv

This is a summary of the risk management plan (RMP) for Maapliv. The RMP details the important risks of Maapliv and how these risks can be minimised.

Maapliv summary of product characteristics (SmPCs) and its package leaflet give essential information to healthcare professionals and patients on how Maapliv should be used.

This summary of the RMP for Maapliv should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary.

I. The medicine and what it is used for.

Maapliv is indicated for the treatment of maple syrup urine disease (MSUD) presenting with an acute decompensation episode in patients from birth who are not eligible for an oral and enteral branched-chain amino acids free (BCAA- free) formulation.

Maapliv is administered by intravenous route.

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

There are no important risks associated with Maapliv. General measures to ensure the use of the product and to learn more about Maapliv's safety are outlined below.

Measures to minimise the risks identified for medicinal products include:

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

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is continuously collected and regularly analysed so that immediate action can be taken if necessary. These measures constitute routine pharmacovigilance activities.

II.A List of important risks and missing information

Important risks of Maapliv are risks that need special surveillance for further investigation, so that the medicinal product can be safely administered. 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 Maapliv. 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).

For Maapliv there are following important safety concerns that need to be included in the current RMP version.

Table 5: List of Important Risks and Missing Information

Important identified risks	• None
Important potential risks	• None
Missing information	• Long-term safety

II.B Summary of important risks

Missing Information: Long term safety	
Risk minimization measures	Routine risk minimization measures • SmPC 4.4 and section 2 of the PI mentions that there is limited information on the repeated administration of the intravenous BCAA-free formula Additional risk minimization measures • No risk minimization measures
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • No additional pharmacovigilance activities

II.C Post-authorisation development plan

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

Purpose of the study: To collect additional data aiming at monitoring the safety and efficacy of Maapliv in a real-world setting through a registry of patients with MSUD treated with MAAPLIV during acute metabolic decompensation episodes to characterise efficacy and safety outcomes.

Rationale: The efficacy and safety of MAAPLIV needs to be further evaluated in this registry and will provide additional information on characteristics on responders/non-responders, decompensation episode outcomes per MSUD subtype, and confirm the safety profile.

Objectives:

- Primary Objectives: Characterise safety and efficacy outcomes on MAAPLIV during acute metabolic decompensation episodes.
- Secondary objectives:

  1. Describe the association between plasma leucine levels and clinical symptom resolution

  2. Describe the characteristics of responders/non-responders* patients per episode to MAAPLIV: responders are patients with a normalisation of leucine ≤ 5mg/dL or 381µmol/L)

  3. Describe the acute decompensation episode outcomes per MSUD subtypes, or per disease severity (i.e. leucine level at baseline)

4. Describe therapeutic management of acute decompensation episodes: hospitalization (duration, unit), decompensation episode treatments (including emergency diet management, MAAPLIV and other concomitant treatments).

5. Evaluate real-world treatment healthcare resource utilization (HRU).

6. Measure the health-related quality of life outcomes for patients and caregivers.

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

NA

7. PART VII: ANNEXES

7.1 Annex 1 Eudravigilance interface

7.2 Annex 2 Tabulated summary of planned, ongoing, and completed pharmacovigilance study programmes

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

7.4 Annex 4 Specific adverse drug reaction follow-up forms

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

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

7.7 Annex 7 Other supporting data (including referenced material)

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

7.1. Annex 1 - EudraVigilance interface

Not applicable.

7.2. Annex 2 - Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme

Not applicable.

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

Not applicable.

7.4. Annex 4 - Specific adverse drug reaction follow-up forms

Not applicable.

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

Protocol will be submitted during first quarter of 2026.

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

Not applicable.

7.7. Annex 7 - Other supporting data (including referenced material)

External references**,** available upon request.

1. T Brosnan. The fourth workshop on the assessment of adequate intake of dietary amino acids: general discussion of sessions 1 and 2. J Nutr. 2005;135(6):1576S-9S.
2. E Simon, U Wendel, P Schadewaldt. Maple syrup urine disease-treatment and outcome in patients of Turkish descent in Germany. Turk J Pediatr. 2005;47 (1):8-13.
3. DH Morton, KA Strauss, DL Robinson, EG Puffenberger, RI Kelley. Diagnosis and treatment of maple syrup disease: a study of 36 patients. Pediatrics. 2002;109(6):999-1008.
4. Strauss KA, Wardley B, Robinson D, Hendrickson C, Rider NL, Puffenberger EG, et al. Classical maple syrup urine disease and brain development: principles of management and formula design. Mol Genet Metab. 2010;99(4):333-45.
5. I Knerr, N Weinhold, J Vockley, KM Gibson. Advances and challenges in the treatment of branched-chain amino/keto acid metabolic defects. J Inherit Metab Dis. 2012;35 (1):29-40.
6. Villani GR, Gallo G, Scolamiero E, Salvatore F, Ruoppolo M. Classical organic acidurias: diagnosis and pathogenesis. Clin Exp Med. 2017;17(3):305-23.
7. Goyanes A, Madla CM, Umerji A, Duran Piñeiro G, Giraldez Montero JM, Lamas Diaz MJ, et al.Automated therapy preparation of isoleucine formulations using 3D printing for the treatment of MSUD: First single-centre, prospective, crossover study in patients. Int J Pharm. 2019;567:118497.

8. Maple syrup urine disease. The portal for rare diseases and orphan drugs. [Internet]. [cited 2023 May 29]. Available from: https://www.orpha.net/consor/www/cgi-bin/Disease_Search.php?lng=EN&data_id=708&Disease_Disease_Search_diseaseGroup=Maple-syrup-urine-disease&Disease_Disease_Search_diseaseType=Pat&Disease%28s%29%2Fgroup+of+diseases=Maple-syrup-urine-disease&title=Maple+syrup+urine+disease&search=Disease_Search_Simple
9. Quinonez SC, Seeley AH, Seeterlin M, Stanley E, Ahmad A. Newborn screening for dihydrolipoamide dehydrogenase deficiency: Citrulline as a useful analyte. Mol Genet Metab Rep. 2014;1:345-9.
10. Blackburn PR, Gass JM, Vairo FPE, Farnham KM, Atwal HK, Macklin S, et al. Maple syrup urine disease: mechanisms and management. Appl Clin Genet. 2017;10: 57-66.
11. Strauss KA, Carson VJ, Soltys K, Young ME, Bowser LE, Puffenberger EG, et al. Branched-chain α-ketoacid dehydrogenase deficiency (maple syrup urine disease): Treatment, biomarkers, and outcomes. Mol Genet Metab. 2020;129 (3):193-206.
12. MT Abi-Warde, C Roda, JB Arnoux, A Servais, F Habarou, A Brassier, et al. Long-term metabolic follow-up and clinical outcome of 35 patients with maple syrup urine disease. J Inherit Metab Dis. 2017;40(6):783-92.
13. P de Lonlay, R Posset, U Mutze, K Mention, D Lamireau, M Schiff, et al. Real-world management of maple syrup urine disease (MSUD) metabolic decompensations with branched chain amino acid-free formulas in France and Germany: A retrospective observational study. JIMD Rep. 2021;59(1):110-19.
14. JM Alili, MP Berleur, MC Husson, K Mention, M Schiff, JB Arnoux, et al. Intravenous administration of a branched-chain amino-acid-free solution in children and adults with acute decompensation of maple syrup urine disease: a prospective multicentre observational study. Orphanet J Rare Dis. 2022;17(1):202.
15. Protocole National de Diagnostic et de Soins (PNDS) Leucinose. 2021 [document on the internet] [accessed 2023 May 10]. Available from: https://www.has-sante.fr/upload/docs/application/pdf/2021-05/pnds_msud_vf.docx.pdf
16. De Castro-Hamoy LG, Chiong MA, Estrada SC, Cordero CP. Challenges in the management of patients with maple syrup urine disease diagnosed by newborn screening in a developing country. J Community Genet. 2017; 8(1):9-15.
17. Xu J, Jakher Y, Ahrens-Nicklas RC. Brain Branched-Chain Amino Acids in Maple Syrup Urine Disease: Implications for Neurological Disorders. Int J Mol Sci. 2020; 21(20):7490.
18. Maple Syrup Urine Disease. 2020. [document on the internet] [accessed 2023 May 17]. Available from: https://rarediseases.org/rare-diseases/maple-syrup-urine-disease/
19. Maple Syrup Urine Disease (MSUD). Children's Hospital of Philadelphia [document on the internet] [accessed 2023 May 17]. Available from: https://www.chop.edu/conditions-diseases/maple-syrup-urine-disease-msud

20. Strauss KA, Puffenberger EG, Carson VJ. Maple Syrup Urine Disease. 2006. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1319/
21. A Servais, JB Arnoux, C Lamy, A Hummel, N Vittoz, I Katerinis, et al. Treatment of acute decompensation of maple syrup urine disease in adult patients with a new parenteral amino-acid mixture. J Inherit Metab Dis. 2013;36(6):939-44.
22. DM Frazier, C Allgeier, C Homer, BJ Marriage, B Ogata, F Rohr, et al. Nutrition management guideline for maple syrup urine disease: an evidence- and consensus-based approach. Mol Genet Metab. 2014; 112(3):210-7.
23. P Sanchez-Pintos, S Meavilla, MG Lopez-Ramos, A Garcia-Cazorla, ML Couce. Intravenous branched-chain amino-acid-free solution for the treatment of metabolic decompensation episodes in Spanish pediatric patients with maple syrup urine disease. Front Pediatr. 2022;10:969741.
24. S Blanco Dorado. ParenteralNutrition with Blanched Chain Aminoacids-free Solution for the Urgent Management of Maple Syrup Urine DiseaseMetabolic Decompensation. Journal. 2017; 41 (3)
25. Townsend I, Kerr DS. Total parenteral nutrition therapy of toxic maple syrup urine disease. Am J Clin Nutr. 1982;36 (2):359-65.
26. Berry GT, Heidenreich R, Kaplan P, Levine F, Mazur A, Palmieri MJ, et al. Branched-chain amino acid-free parenteral nutrition in the treatment of acute metabolic decompensation in patients with maple syrup urine disease. N Engl J Med. 1991;324 (3):175-9.
27. Morton DH, Strauss KA, Robinson DL, Puffenberger EG, Kelley RI. Diagnosis and treatment of maple syrup disease: a study of 36 patients. Pediatrics. 2002;109(6): 999-1008.
28. Couce Pico ML, Castineiras Ramos DE, Boveda Fontan MD, Iglesias Rodriguez AJ, Cocho de Juan JA, Fraga Bermudez JM. Advances in the diagnosis and treatment of maple syrup urine disease: experience in Galicia (Spain). Anales de pediatria. 2007; 67(4):337-43.
29. Vikram CM., Tripathi A., Kalita, S., Prasanna, SM. (2018, September). Estimation of Hypernasality Scores from Cleft Lip and Palate Speech. In Interspeech (pp. 1701-1705).
30. Hoffer LJ. Parenteral Nutrition: Amino Acids. Nutrients. 2017; 9(3):257
31. Maple syrup urine disease - symptoms, causes, treatment: Nord [Internet]. 2023 [cited 2023 May 29]. Available from: https://rarediseases.org/rare-diseases/maple-syrup-urine-disease/

7.8. Annex 8 - Summary of changes to the risk management plan over time

A list of significant changes to this RMP for Maapliv over time is provided with the below table:

List of Significant Changes to the Risk Management Plan Over Time		
Version	**Procedure Approval Date**	**Change**
1.0	Marketing authorization application – 14 June 2023	Not applicable – new RMP.
1.3	Marketing authorization – DDMMM2025	**Safety concerns** The following safety concern was included in the list of missing information: • Long term safety **Post-authorization efficacy plan** Post authorization efficacy plan updated to include registry study.