28 May 2025
EMA/OD/0000152027
EMADOC-1700519818-2469338 **Corr.**[1]
Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

of an orphan medicinal product submitted for marketing authorisation application

Maapliv (Glycine, L-alanine, L-arginine, L-aspartic acid, L-cysteine, L-glutamic acid, L-histidine, L-lysine monohydrate, L-methionine, L-phenylalanine, L-proline, L-serine, L-threonine, L-tryptophan, L-tyrosine, taurine)
Treatment of maple syrup urine disease
EU/3/18/2076

Sponsor: Recordati Rare Diseases

Note

Assessment report as adopted by the COMP with all information of a commercially confidential nature deleted.

[1] Corrigendum of OMAR EMADOC-1700519818-2185477: Update of active substance, page 10.

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1. Product and administrative information

Product	
Designated active substance(s)	Glycine, L-alanine, L-arginine, L-aspartic acid, L-cysteine, L-glutamic acid, L-histidine, L-lysine monohydrate, L-methionine, L-phenylalanine, L-proline, L-serine, L-threonine, L-tryptophan, L-tyrosine, taurine
Other name(s)	Maapliv, Glycine, L-alanine, L-arginine, L-aspartic acid, L-cysteine, L-glutamic acid, L-histidine, L-lysine monohydrate, L-methionine, L-phenylalanine, L-proline, L-serine, L-threonine, L-tryptophan, L-tyrosine, taurine, ODD EU/3/18/2076 amended to exclude L-cystine
International Non-Proprietary Name	Amino acids
Tradename	Maapliv
Orphan condition	Treatment of maple syrup urine disease
Sponsor's details:	Recordati Rare Diseases Immeuble Le Wilson 70 Avenue Du General De Gaulle 92800 Puteaux France
Orphan medicinal product designation procedural history	
Sponsor/applicant	Recordati Rare Diseases
COMP opinion	13 September 2018
EC decision	26 October 2018
EC registration number	EU/3/18/2076
Post-designation procedural history	
Sponsor's name change	Name change from Orphan Europe SARL to Recordati Rare Diseases – EC letter of 10 July 2019
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Ewa Balkowiec Iskra / Jayne Crowe
Applicant	Recordati Rare Diseases
Application submission	8 September 2023
Procedure start	28 September 2023
Procedure number	EMA/H/C/005557/0000
Invented name	Maapliv

Therapeutic indication	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 Further information on Maapliv can be found in the European public assessment report (EPAR) on the Agency's website :https://www.ema.europa.eu/en/medicines/human/EPAR/Maapliv
CHMP opinion	22 May 2025

COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Vallo Tillmann/Joao Rocha
Sponsor's report submission	8 September 2023
COMP discussion	13-15 May 2025
COMP opinion (adoption via written procedure)	28 May 2025

2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product in 2018 designation was based on the following grounds:

- the intention to treat the condition with the medicinal product containing glycine, L-alanine, L-arginine, L-aspartic acid, L-cysteine, L-glutamic acid, L-histidine, L-lysine monohydrate, L-methionine, L-phenylalanine, L-proline, L-serine, L-threonine, L-tryptophan, L-tyrosine, taurine was considered justified based on clinical observations in affected patients with acute decompensation who responded to treatment with the proposed product;
- the condition is chronically debilitating due to psychomotor delay and life-threatening in particular due to decompensation episodes leading to progressive encephalopathy and cerebral oedema;
- the condition was estimated to be affecting less than 0.1 in 10,000 persons in the European Union, at the time the application was made.

Thus, the requirements under Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled.

The sponsor has also established that there exists no satisfactory method of in the European Union for patients affected by the condition.

Thus, the requirement under Article 3(1)(b) of Regulation (EC) No 141/2000 on orphan medicinal products is fulfilled.

3. Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

Maple Syrup Urine Disease (MSUD), also known as branched-chain ketoaciduria, is a rare autosomal recessive metabolic disorder characterized by a deficiency in the branched-chain alpha-ketoacid dehydrogenase (BCKD) (Campo et al, 2016). This enzyme complex is responsible for the decarboxylation of branched-chain alpha-ketoacids, the second step in the catabolism of the essential branched-chain amino acids (BCAAs): leucine, isoleucine, and valine. A deficiency in BCKD activity leads to the accumulation of these amino acids and their corresponding ketoacids in body fluids, resulting in neurotoxicity and a distinct metabolic profile.

The human BCKD is a large multienzyme complex with a molecular mass of approximately 4.5 MDa and consists of three primary catalytic components: a heterotetrametric branched-chain α-ketoacid decarboxylase (E1), a homo-24-meric dihydrolipoyl transacylase (E2), and a homodimeric dihydrolipoamide dehydrogenase (E3) (Knerr et al, 2012; Strauss et al, 2010). Proper function of this complex depends on regulation via the phosphorylation status of the E1α subunit. This regulation is mediated by two associated enzymes: BCKD kinase (BCKDK), which inactivates the complex via phosphorylation, and BCKD phosphatase (BCKDP, also known as PPM1K), which reactivates it through dephosphorylation.

Genetically, MSUD is caused by pathogenic variants in one of three genes: BCKDHA, encoding the E1α subunit; BCKDHB, encoding the E1β subunit; and DBT, encoding the E2 subunit. Rarely, mutations in DLD, which encodes the E3 subunit, can result in an E3-deficient variant of the disease. These genetic disruptions lead to diminished or absent enzymatic activity of the BCKD, impairing the degradation of BCAAs and leading to toxic accumulation. Biochemical hallmarks of the disease include elevated levels of leucine, isoleucine, and valine in plasma; increased levels of their corresponding alpha-ketoacids in urine; and the presence of alloisoleucine, a diagnostic biomarker not normally found in healthy individuals.

Clinically, MSUD presents with a wide spectrum of phenotypes, and currently, there is no well-defined correlation between genotype and clinical severity (Strauss et al, 2013; Carecchio et al, 2011). Five major clinical forms of MSUD are recognized. The classic form, the most severe and common, typically manifests within the first few days of life with symptoms such as poor feeding, lethargy, irritability, and a distinctive maple syrup odour in the urine. Without prompt diagnosis and treatment, affected neonates may rapidly deteriorate, developing seizures, coma, and potentially fatal encephalopathy. E3-deficient MSUD, while also presenting in infancy, includes additional systemic manifestations due to the broader role of the E3 enzyme in multiple mitochondrial dehydrogenase complexes. Intermediate MSUD has a later onset with milder symptoms and partial BCKD activity. Intermittent MSUD is characterized by normal development and metabolism under baseline conditions, with episodic metabolic crises during physiological stress or illness. Thiamine-responsive MSUD represents a milder variant where residual enzyme activity can be augmented by pharmacological doses of thiamine.

MSUD requires early recognition and lifelong management to prevent metabolic decompensation, which can be triggered by catabolic stress, infection, or dietary indiscretion (Simon et al, 2006; Morton et al, 2002). Diagnosis is confirmed through plasma amino acid analysis, and molecular genetic testing.

The proposed therapeutic indication "treatment of acute decompensation episodes with maple syrup urine disease (MSUD) who are not eligible for an oral BCAA- free formulation. Maapliv is indicated in adults and children aged from 0 to 18 years." falls entirely within the orphan condition "Treatment of maple syrup urine disease".

Intention to diagnose, prevent or treat

The medical plausibility has been confirmed by the positive benefit/risk assessment of the CHMP, see EPAR.

Chronically debilitating and/or life-threatening nature

The sponsor argues that the condition remains to be life-threatening and chronically debilitating due to the accumulation of branched-chain amino acids (BCAAs) and their corresponding ketoacids (BCKAs) MSUD which exert significant neurotoxic effects. During episodes of metabolic decompensation - often

triggered by catabolic stress such as infection, fasting, surgery, or trauma - the buildup of these metabolites can reach toxic levels (Servais et al, 2013; Berry et al, 1991). If not promptly recognized and treated, such episodes can result in severe cerebral oedema, presenting clinically with rapidly progressive encephalopathy. This may progress to central transtentorial herniation, a fatal complication that reflects the vulnerability of the central nervous system to BCAA and BCKA toxicity (Osgood et al, 2015; Villani et al, 2017).

The acute risks are compounded by the long-term effects of recurrent or sustained exposure to elevated BCAA levels. Chronically, individuals with MSUD are at risk of progressive neurological deterioration and psychiatric complications (Villani et al, 2017). This includes cognitive impairment, psychomotor delays, behavioural disturbances, and mood disorders. These outcomes are particularly severe in patients who experience recurrent metabolic crises or those in whom the condition is inadequately managed.

Recognizing the severity of the condition, the Committee for Orphan Medicinal Products (COMP) has concluded that MSUD remains a chronically debilitating and life-threatening disorder. This conclusion is based on the persistent risk of psychomotor impairment, the potential for rapid neurological decline during metabolic decompensation, and the high risk of mortality associated with cerebral oedema and encephalopathy. These clinical characteristics have remained unchanged since the original designation of the condition.

Therefore, the classification of MSUD as both chronically debilitating and life-threatening remains justified.

Number of people affected or at risk

At the time of initial orphan designation, it was concluded that the condition was estimated to be affecting less than 0.1 in 10,000 persons in the European Union. At the present time of the maintenance of the orphan designation, the sponsor's prevalence estimation strategy for Maple Syrup Urine Disease (MSUD) is based on recent epidemiological data obtained through national newborn screening programmes across multiple EU/EEA member states. These data indicate regional variability in incidence, ranging from approximately 1:52,541 to 1:491,000 live births.

Recent national estimates from population-based screening include:

- Italy: 1:201,692 (2019–2020) (Ruoppolo, Malvagia et al. 2022)
- The Netherlands: 1:491,000 (2007–2017) (Stroek, Boelen et al. 2020)
- Spain: 1:197,607 in Madrid (2011–2019) (Martín-Rivada, Palomino Pérez et al. 2022), with a notably higher incidence of 1:52,541 in North-West Spain (Couce, Castiñeiras et al. 2011)
- France: Estimated between 1:100,000 and 1:200,000 (Touati, Gorce et al. 2021)
- Germany: 1:177,978 (2000–2014) (Chapman, Gramer et al. 2018)
- Ireland: 1:147,975 (1972–2018) (O'Reilly, Crushell et al. 2021)

Taking into account the population distribution across the EU/EEA, the sponsor estimates the incidence of MSUD at approximately 1 in 185,000 live births.

Applying this incidence to the most recent EU birth statistics — 3.67 million live births in 2023 (Eurostat, 2025) - approximately 26 new cases of MSUD are expected annually within the EU/EEA.

Given the improvement in life expectancy resulting from early diagnosis and management (including newborn screening, specialized dietary treatment, and liver transplantation) (Strauss, Wardley et al. 2010), the sponsor has translated incidence into prevalence using standard epidemiological methodology:

- Prevalence = Incidence × Average Disease Duration

Assuming a conservative disease duration of 50 years this results into approximately 278 cases per 10 million people, or a prevalence of 0.3 per 10,000 persons.

This updated, population-weighted epidemiological analysis based on national newborn screening data across the EU/EEA supports an estimated MSUD prevalence of 0.3 per 10,000 persons. The COMP agreed with this prevalence calculation and concluded that these findings support the continued eligibility of MSUD for orphan medicinal product designation under EU legislation.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

Currently, there are no authorized pharmacological treatments specifically approved for Maple Syrup Urine Disease (MSUD). Management of the condition remains primarily supportive and is centred on strict dietary restriction of branched-chain amino acids (BCAAs), combined with prompt intervention during episodes of metabolic decompensation. These interventions are designed to reduce the accumulation of toxic metabolites and to prevent irreversible neurological damage or death.

Several orphan designations have been granted by the COMP. However, as of now, these products have not received marketing authorization.

Acute metabolic decompensations are managed in accordance with established clinical guidelines, such as those outlined by Rodan et al. (2018). These episodes require immediate intervention with high-calorie intake—typically delivered via intravenous glucose and lipids—to suppress catabolism and promote anabolism. Simultaneously, patients are given BCAA-free amino acid formulas either orally or parenterally to maintain protein intake while minimizing toxic metabolite accumulation. In severe or refractory cases, extracorporeal methods, including haemodialysis or hemofiltration, are employed to rapidly reduce plasma leucine levels and prevent cerebral oedema (Rodan LH et al., Pediatr Emerg Care. 2018 Jan;34(1):64–67).

The sponsor has identified a range of nutritional and supportive therapies currently available in the European Union for the management of MSUD. These include BCAA-free medical nutrition products. In addition, hospital-compounded nutrient-enriched BCAA-free formulas for enteral and parenteral administration are used. Thiamine supplementation may be beneficial in patients with thiamine-responsive MSUD, a milder variant in which residual enzyme activity can be enhanced by cofactor therapy.

For individuals with frequent decompensation or poor metabolic control despite optimal medical therapy, liver transplantation remains a definitive treatment option. Transplantation provides a continuous source of functional BCKDC enzyme activity, offering metabolic stabilization and reducing the risk of future decompensations.

Significant benefit

Not applicable.

4. COMP position adopted on 28 May 2025

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product.
- the prevalence of maple syrup urine disease (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be less than 0.3 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is chronically debilitating due to psychomotor delay and life-threatening in particular due to decompensation episodes leading to progressive encephalopathy and cerebral oedema;
- at present, no satisfactory method for the treatment of the condition has been authorised in the European Union for patients affected by the condition.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Maapliv, glycine, L-alanine, L-arginine, L-aspartic acid, L-cysteine, L-glutamic acid, L-histidine, L-lysine monohydrate, L-methionine, L-phenylalanine, L-proline, L-serine, L-threonine, L-tryptophan, L-tyrosine, taurine for treatment of maple syrup urine disease (EU/3/18/2076) is not removed from the Community Register of Orphan Medicinal Products.