

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Maapliv solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 500 mL of solution contains 26.375 g of amino acids.

Active substance	For 500 mL (one bottle)
L-alanine	3.15 g
L-arginine	2.05 g
L-aspartic acid	2.05 g
L-cysteine hydrochloride monohydrate (equivalent to L-cysteine)	0.725 g (0.50 g)
L-glutamic acid	3.55 g
Glycine	1.05 g
L-histidine	1.05 g
L-lysine monohydrate (equivalent to L-lysine)	3.15 g (2.80 g)
L-methionine	0.65 g
L-phenylalanine	1.35 g
L-proline	2.80 g
L-serine	1.90 g
Taurine	0.15 g
L-threonine	1.80 g
L-tryptophan	0.70 g
L-tyrosine	0.25 g

Caloric value: 206 Kcal/L

Osmolality: 475 mOsmol/Kg

pH: 5.2

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion.

Clear solution free of particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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.

4.2 Posology and method of administration

Treatment with Maapliv should be initiated under the supervision of a physician experienced in the management of MSUD disease.

There is a limited experience in patients with severe or critical elevation in leucine levels and therefore caution is required in these patients. In these patients the intravenous BCAA-free formula may be insufficient to adequately lower leucine levels and they may require other treatments such as haemodialysis or haemofiltration.

Posology

The dose of Maapliv should be individualised based on the patient's ability to adequately metabolise amino acids, age, body weight and nutritional/fluid requirements, as well as additional energy given orally/enterally to the patient.

A sufficient calorie intake must be concomitantly provided with the amino acid administration. It may consist of concomitant infusions of glucose and lipid solution; it must be at least equal to the calorie intake adjusted to the patient's age.

Careful supplementation with isoleucine and valine should also be consistently added; if no solution for infusion is available with these 2 amino acids they can be administered by oral or enteral route.

In all cases, the infusion should be determined by a physician experienced in MSUD and intravenous therapy.

A continuous infusion is recommended.

The treatment with Maapliv may be maintained until the resolution of the decompensation episode (leucine plasma level below 381 µmol/L).

Adult population

The recommended daily dose range in adults is provided in Table 1.

Table 1: Guidance on the dose for administration in adults

Amino acid dose per 24 hours	Volume per 24 hours	Volume per hour
1 to 2 g/kg	19 to 39 mL/kg	0.8 to 1.6 mL/kg

Paediatric population

The recommended daily dose range in the paediatric population is described in Table 2.

Table 2: Guidance on the doses for administration in paediatric patients

Patient's age	Amino acid dose per 24 hours	Volume per 24 hours	Volume per hour
Newborn infants, infants and toddlers up to 23 months	2 to 3 g/kg	39 to 58 mL/kg	1.6 to 2.4 mL/kg
Child, adolescent	1 to 2 g/kg	19 to 39 mL/kg	0.8 to 1.6 mL/kg

Dose adjustment of Maapliv is dependent on the patient's age and body weight. Leucine levels determine the overall treatment approach and total nutritional regimen, for example if the patient needs to undergo haemodialysis/haemofiltration for severe or persistently elevated leucine levels.

During acute decompensation consider adjusting the dose daily as needed based on leucine levels. Once stabilized consider adjusting every 2-3 days as needed.

Method of administration

Continuous central or peripheral intravenous infusion.

Considering osmolality, peripheral route is possible but must be limited to a few days to limit the risk of thrombophlebitis at the infusion site.

Maapliv is a hypertonic solution that should be administered at slow infusion rate (see tables 1 and 2).

Keep the bottle protected from light during administration.

For instructions on handling of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

In severe/critical acute decompensation episodes treatment with intravenous BCAA-free amino acid formulation may be insufficient and other treatments, for example haemodialysis or haemofiltration may need to be considered/implemented.

Outcome measures beyond leucine levels were not systematically reported in the Maapliv clinical study programme, thus the impact of treatment with intravenous BCAA-free formula on symptom improvement or other aspects of clinical status is currently unknown.

There is limited information on the repeated administration of the intravenous BCAA- free formula.

It is essential to provide adequate calories concurrently if parenterally administered amino acids are to be retained by the body and utilized for protein synthesis.

Severe water and electrolyte disorders, severe fluid overload states, and severe metabolic disorders should be corrected before starting the infusion.

Clinical and laboratory monitoring is required, especially at the beginning of the intravenous infusion. Monitoring should include assessment of fluid and electrolyte balance, serum osmolality, acid-base balance, blood glucose, blood ammonia, serum proteins and hepatic and renal functions.

Maapliv is a hypertonic solution that should be administered at slow infusion rate (see section 4.2).

Precautions for infusion therapy or parenteral nutrition

General precautions for infusion therapy or parenteral nutrition apply to this medicinal product (e.g. acute pulmonary oedema, hyperhydration, acute phase of circulatory shock).

The administration of intravenous solutions can cause fluid and/or solute overload resulting in dilution of serum electrolyte concentrations, overhydration, congested states, or pulmonary oedema. The risk of dilutional states is inversely proportional to the electrolyte concentrations of the solutions.

Cardiovascular impairment

Caution shall be exercised in patients with severe heart failure by maintaining an appropriate balance between the volumes of fluids excreted and fluids introduced.

Renal impairment

The administration of amino acids in the presence of impaired renal function may increase an already elevated blood urea nitrogen. Patients with azotaemia from any cause should not be infused with amino acids without regard to total nitrogen intake. Fluid and electrolyte status should be closely monitored for water and/or electrolyte retention and managed appropriately. Caution should be taken in order to balance the total volumes introduced and the total volumes excreted.

Hepatic impairment

The administration of amino acid solutions to a patient with severe hepatic insufficiency may result in plasma amino acid imbalances, hyperammonaemia, stupor and coma. Amino acid solutions should be used with caution in patients with pre-existing liver disease or liver insufficiency. Liver function parameters should be closely monitored in these patients, and they should be monitored for possible symptoms of hyperammonaemia. Should symptoms of hyperammonaemia develop, amino acid administration should be discontinued and the patient's clinical status re-evaluated.

Anaphylactic reactions

Anaphylactic/anaphylactoid reactions have been reported with amino acid solutions administered as a component of parenteral nutrition (see section 4.8). The infusion must be stopped immediately if any signs or symptoms of hypersensitivity reaction develop.

Thromboembolism

Pulmonary vascular precipitates causing pulmonary vascular emboli and pulmonary distress have been reported in patients receiving parenteral nutrition. If signs of pulmonary distress occur, the infusion should be stopped and medical evaluation initiated.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed to date. Amino acid solutions may precipitate acute folate deficiency and folic acid should be given daily.

4.6 Fertility, pregnancy, and lactation

Pregnancy

There are no clinical data from the use of Maapliv in pregnant women. No animal reproductive studies have been performed with Maapliv (see section 5.3).

Maapliv is not recommended during pregnancy unless the clinical condition of the woman clearly requires this treatment and only after a careful risk-benefit consideration.

Breast-feeding

Amino acids/metabolites are excreted in human milk. At therapeutic doses of Maapliv no effects on the breastfed neonate/infant are expected. However, Maapliv should be used during breast-feeding only after a careful risk-benefit consideration.

There is insufficient information on the excretion of Maapliv components/metabolites in human milk. A risk to the newborns/infants cannot be excluded.

Fertility

No adequate data are available. At therapeutic doses, no effects are anticipated.

4.7 Effects on ability to drive and use machines

Maapliv has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The class-like adverse reactions listed below have been identified from the available medical literature with the parenteral administration of branched chained amino acid-free solutions and parenteral nutrition.

Tabulated list of adverse reactions

Adverse reactions are summarised in the table below. These adverse reactions are presented by MedDRA system organ class and frequency. Frequency categories are defined as: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1\ 000$ to $< 1/100$), rare ($\geq 1/10\ 000$ to $< 1/1\ 000$), very rare ($< 1/10\ 000$) and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 3: Summary of adverse reactions

System organ class	Uncommon
Immune system disorders	Anaphylactic/anaphylactoid reactions, hypersensitivity.
Metabolism and nutrition disorders	Hyperammonaemia.
Vascular disorders	Thromboembolism pulmonary embolism, venous thromboembolism and respiratory distress).
Hepatobiliary disorders	Blood bilirubin increased, hepatic enzyme increased, cholestasis, cholecystitis, cholelithiasis.
Renal and urinary disorders	Azotaemia.
General disorders and administration site conditions	Infusion site thrombophlebitis; venous irritation.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit / risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

4.9 Overdose

As with other amino acid solutions, overdose may induce the following adverse reactions:

- Symptoms of fluid retention: Overdose or high rate of infusion may lead to fluid overload / retention, electrolytic disturbances, and acute pulmonary oedema.

- Symptoms of amino acid overdose: Overdose or high rate of infusion may lead to adverse reactions such as shivering, vomiting, headache, nausea, hyperammonaemia and increased renal amino acid losses.

If there are signs of overdose the infusion should be stopped immediately and may be resumed with a reduced dose or slower infusion rate.

There is no specific antidote for overdose. Emergency procedures should include appropriate corrective measures.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Blood substitutes and perfusion solutions. Solutions for parenteral use, ATC code: B05BA01

Maapliv is a branched chain amino acid-free amino acid solution intended to provide 7 essential and 9 non-essential amino acids as physiological substrates for protein synthesis.

In patients with MSUD decompensation, BCAA-free solution in combination with carbohydrate and lipid supplementation prevents or reverses protein catabolism and promotes anabolism, reducing the corresponding alpha-keto acid levels.

The Maapliv clinical study programme is based on 4 retrospective studies involving patients with maple syrup urine disease (MSUD) who received intravenous branched-chain amino acid (BCAA)-free solution for acute decompensation episodes.

Study 1. Servais et al. 2013

Study design: Retrospective comparison study. **Population:** 4 adult MSUD patients (17 decompensation episodes treated with parenteral amino-acid mixture vs 18 previous episodes treated by enteral feeding). **Treatment:** Parenteral amino-acid mixture (group P) vs enteral feeding (group E). **Primary objective:** Evaluate efficacy of parenteral amino-acid mixture in reducing leucine concentration. **Results:** Mean leucine concentration at presentation: 1 196.9 $\mu\text{mol/L}$ (group P) vs 1 212.2 $\mu\text{mol/L}$ (group E). Mean leucine decrease in first 3 days was significantly higher in group P ($p = 0.0026$). Mean hospitalization duration: 4 days (group P) vs 4.5 days (group E) ($p = \text{NS}$). No side effects reported in group P. One patient in group E required dialysis, while no patients in group P deteriorated.

Study 2. de Lonlay et al. 2021

Study design: Retrospective observational study. **Population:** 54 MSUD patients (126 decompensation episodes) from 5 centers in France and Germany (2010-2016). **Treatment:** Enteral/oral vs intravenous BCAA-free formula. **Primary objective:** Describe episodes and outcomes for patients receiving enteral/oral or intravenous BCAA-free formula. **Results:** Mean hospitalization duration: 6.6 days (oral/enteral) vs 5.4 days (IV). Mean leucine level decrease: 548.5 $\mu\text{mol/L}$ (69.3%) in oral/enteral group vs 657.2 $\mu\text{mol/L}$ (71.3%) in intravenous group. In the adult subgroup, mean time to episode resolution was 15.8 days (oral/enteral) vs 7.7 days (intravenous) ($p = 0.008$) and mean hospitalization duration was 6 days (oral/enteral) vs 4.6 days (intravenous) ($p = \text{NS}$). Seven serious adverse events reported in two patients; only nausea and vomiting were treatment-related.

Study 3. Sánchez-Pintos et al. 2022

Study design: Paediatric case series. **Population:** 5 MSUD paediatric patients (5 decompensation episodes + 1 prophylactic use for surgery). **Treatment:** intravenous BCAA-free solution. **Primary objective:** Evaluate management of decompensation episodes with the intravenous BCAA-free solution. **Results:** Leucine levels at admission: 699-3 296 $\mu\text{mol/L}$. Leucine normalization was achieved in all cases. Duration of administration: 3-20 days. No related adverse events observed.

Study 4. Alili et al. 2022

Study design: Observational prospective study. **Population:** 24 MSUD patients (16 males, 8 females; 126 decompensation episodes: 39 in children, 87 in adults). **Treatment:** intravenous BCAA-free solution. **Primary objective:** Evaluate effectiveness and safety of intravenous BCAA-free solution in managing metabolic decompensations. **Results:** At presentation, mean leucine plasma concentration was $\geq 381 \mu\text{mol/L}$ in 113/126 (89.7%) episodes. Leucine normalization (to below 381 $\mu\text{mol/L}$): 82% (18/22) of episodes in children, 84% (67/80) of episodes in adults. Mean time to leucine normalization: 3.0 days (significantly shorter than predicted time with traditional methods, $p < 0.001$). Mean hospitalization duration: 7.1 days (children) vs 5.2 days (adults) ($p = 0.012$). No treatment-related adverse events reported. Dose: children treated with 0.8 to 2.0 g/kg/day for 4.8 days; adults treated with 0.5 to 2.6 g/kg/day for 3.8 days.

Outcome measures other than leucine levels were not systematically reported in the above clinical studies, thus the impact of treatment with Maapliv on symptom improvement or other aspects of clinical status is unknown. The overwhelming majority of patients treated in the Maapliv clinical development programme had a classical form of MSUD. There is no experience with other subtypes of MSUD.

The available data are insufficient to claim a better efficacy as comparing to oral and enteral BCAA-free formulations. The comparative studies between intravenous and oral/enteral BCAA-free formulations have not demonstrated statistically significant differences in efficacy.

This medicinal product has been authorised under ‘exceptional circumstances’.

This means that due to the rarity of the disease it has not been possible to obtain complete information on this medicinal product.

The European Medicines Agency will review any new information which may become available every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

Absorption

Maapliv is administered intravenously. The systemic bioavailability of the free amino acids in the solution is therefore 100%.

Distribution

Initial distribution of most amino acids takes place via the central vascular compartment and extravascular water. Amino acids are transported into cells where their incorporation into proteins, conversion to other amino acids, degradation for fuel or deamination occurs.

Biotransformation

The amino acid solution provides a source of 7 essential and 9 non-essential amino acids for metabolic processes involved in protein synthesis. Amino acids in excess to immediate requirements are either metabolized in alternative pathways, catabolized and / or excreted in sweat and urine.

Elimination

Amino acids are excreted in the renal tubules and an active transport mechanism is responsible for resorbing amino acids from the glomerular filtrate (primarily in the proximal tubules) and returning them to the circulation. There is an upper limit to the capacity of this active transport system, beyond which excess amino acids are excreted in the urine.

5.3 Preclinical safety data

No preclinical data are available for Maapliv.

Amino acids and electrolytes are fundamental and widespread elements in mammalian metabolism and therefore conventional studies with Maapliv have not been performed to evaluate carcinogenic potential, mutagenic potential, or effects on fertility.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Acetic acid or sodium hydroxide (for pH adjustment)
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store in the original package in order to protect from light.
Do not refrigerate or freeze.

6.5 Nature and contents of container

500 mL colourless type II glass bottle.
Each carton contains one bottle.

6.6 Special precautions for disposal and other handling

The bottle containing the solution for infusion should be visually inspected for clarity and integrity (no leaks) before use.

Use only if the solution is clear, without visible particles and if the container is undamaged.

Administer immediately following the insertion of infusion set with 0.2 micron in-line filter.

Respect strict aseptic conditions, the solution should be administered with sterile equipment using an aseptic technique. The equipment should be primed with the solution to prevent air entering the system.

For single use only. Do not reuse the content of a bottle previously opened.

Keep the bottle protected from light during administration.

For method of administration and precautions to be taken before handling or administering the medicinal product, please see also section 4.2.

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

7. MARKETING AUTHORISATION HOLDER

RECORDATI RARE DISEASES

Tour Hekla

52 avenue du Général De Gaulle

92800 Puteaux

France

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/1955/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <https://www.ema.europa.eu>.

ANNEX II

- A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**
- E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES**

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

RECORDATI RARE DISEASES

Tour Hekla
52 avenue du Général De Gaulle
92800 Puteaux
France

RECORDATI RARE DISEASES

Eco River Parc
30 rue des Peupliers
92000 Nanterre
France

Industria Farmaceutica Galenica Senese S.r.l.
Via Cassia Nord, 351,
53014 Monteroni d'Arbia (SI)
Italy

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristic, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

• Periodic safety update reports (PSURs)

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

• Risk management plan (RMP)

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;

- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES

This being an approval under exceptional circumstances and pursuant to Article 14(8) of Regulation (EC) No 726/2004, the MAH shall conduct, within the stated timeframe, the following measures:

Description	Due date
Non-interventional post-authorisation study: In order to further characterise the efficacy and safety of Maapliv in the treatment of patients with maple syrup urine disease (MSUD) presenting with acute decompensation episodes, the MAH should conduct and submit the results of a non-interventional post-authorisation study, according to an agreed protocol	Protocol submission: Q1 2026 Annual reports to be submitted with annual reassessment
In order to ensure adequate monitoring of safety and efficacy of Maapliv in the treatment of patients with maple syrup urine disease (MSUD) presenting with acute decompensation episodes treated, the MAH should provide yearly updates on any new information concerning the safety and efficacy of Maapliv.	Annually (with annual reassessment)

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**CARTON BOX****1. NAME OF THE MEDICINAL PRODUCT**

Maapliv solution for infusion

L-alanine, L-arginine, L-aspartic acid, L-cysteine hydrochloride monohydrate, L-glutamic acid, Glycine, L-histidine, L-lysine monohydrate, L-methionine, L-phenylalanine, L-proline, L-serine, Taurine, L-threonine, L-tryptophan, L-tyrosine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 500 mL of solution contains 26.375 g of amino acids.

Active substance	For 500 mL (one bottle)
L-alanine	3.15 g
L-arginine	2.05 g
L-aspartic acid	2.05 g
L-cysteine hydrochloride monohydrate (equivalent to L-cysteine)	0.725 g (0.50 g)
L-glutamic acid	3.55 g
Glycine	1.05 g
L-histidine	1.05 g
L-lysine monohydrate (equivalent to L-lysine)	3.15 g (2.80 g)
L-methionine	0.65 g
L-phenylalanine	1.35 g
L-proline	2.80 g
L-serine	1.90 g
Taurine	0.15 g
L-threonine	1.80 g
L-tryptophan	0.70 g
L-tyrosine	0.25 g

3. LIST OF EXCIPIENTS

Acetic acid or sodium hydroxide (for pH adjustment), water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for infusion
1 bottle.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only.
Read the package leaflet before use.
Intravenous use.
Keep the bottle protected from light during administration.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN
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Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY
--

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light.
Do not refrigerate or freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE
--

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

RECORDATI RARE DISEASES
Tour Hekla
52 avenue du Général De Gaulle
92800 Puteaux
France

12. MARKETING AUTHORISATION NUMBER(S)
--

EU/1/25/1955/001

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY
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15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

maapliv

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA
--

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING**GLASS BOTTLE****1. NAME OF THE MEDICINAL PRODUCT**

Maapliv solution for infusion

L-alanine, L-arginine, L-aspartic acid, L-cysteine hydrochloride monohydrate, L-glutamic acid, Glycine, L-histidine, L-lysine monohydrate, L-methionine, L-phenylalanine, L-proline, L-serine, Taurine, L-threonine, L-tryptophan, L-tyrosine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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L-alanine	3.15 g
L-arginine	2.05 g
L-aspartic acid	2.05 g
L-cysteine hydrochloride monohydrate (equivalent to L-cysteine)	0.725 g (0.50 g)
L-glutamic acid	3.55 g
Glycine	1.05 g
L-histidine	1.05 g
L-lysine monohydrate (equivalent to L-lysine)	3.15 g (2.80 g)
L-methionine	0.65 g
L-phenylalanine	1.35 g
L-proline	2.80 g
L-serine	1.90 g
Taurine	0.15 g
L-threonine	1.80 g
L-tryptophan	0.70 g
L-tyrosine	0.25 g

3. LIST OF EXCIPIENTS

Acetic acid or sodium hydroxide (for pH adjustment), water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for infusion
500 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only.
Read the package leaflet before use.

Intravenous use.
Keep the bottle protected from light during administration.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light.
Do not refrigerate or freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

RECORDATI RARE DISEASES
Tour Hekla
52 avenue du Général De Gaulle
92800 Puteaux
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/1955/001

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA
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B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Maapliv solution for infusion

L-alanine, L-arginine, L-aspartic acid, L-cysteine hydrochloride monohydrate, L-glutamic acid, Glycine, L-histidine, L-lysine monohydrate, L-methionine, L-phenylalanine, L-proline, L-serine, Taurine, L-threonine, L-tryptophan, L-tyrosine

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Maapliv is and what it is used for
2. What you need to know before you use Maapliv
3. How to use Maapliv
4. Possible side effects
5. How to store Maapliv
6. Contents of the pack and other information

1. What Maapliv is and what it is used for

Maapliv contains amino acids, which belong to a group of medicines called amino acids for parenteral use. It contains the following amino acids:

L-alanine, L-arginine, L-aspartic acid, L-cysteine hydrochloride monohydrate, L-glutamic acid, Glycine, L-histidine, L-lysine monohydrate, L-methionine, L-phenylalanine, L-proline, L-serine, Taurine, L-threonine, L-tryptophan, L-tyrosine.

Maapliv is used to treat maple syrup urine disease (MSUD) in patients from birth. It is used when patients have a sudden worsening of MSUD and cannot take a special diet free of certain amino acids. MSUD is a rare genetic disorder where the body can't break down certain amino acids found in protein. This leads to a buildup of harmful substances in the blood and urine, which can cause serious health problems.

2. What you need to know before you use Maapliv

Do not use Maapliv

- if you are allergic to one of the amino acids or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Inform your doctor if you have:

- heart failure
- reduced kidney function
- reduced liver function
- predisposition to thromboembolism

Before you start treatment your doctor will monitor you and do tests, especially at the beginning of the infusion (drip). These include:

- checking fluid and electrolyte levels;
- serum osmolarity (measure of water and dissolved substances, such as glucose, urea nitrogen and sodium, in the blood);
- acid-base balance (having the right amounts of acids and bases in the blood and other body fluids);
- blood glucose;
- blood ammonia (a normal waste product in your body);
- blood proteins;
- liver and kidney function.

If you have severe water and electrolyte imbalances, too much fluid in the body or a severe metabolic disorder, these will be corrected before you are given the infusion.

Sudden, severe anaphylactic reactions can occur with amino acid solutions, such as Maapliv, that are used for intravenous nutrition. If you develop any signs or symptoms of an allergic reaction during treatment tell your doctor or nurse immediately. These include:

- hives
- rash
- itching
- dizziness
- wheezing
- difficulty breathing
- swelling of the tongue

Patients receiving intravenous nutrition can develop blockages in the blood vessels of the lungs. If you develop any signs or symptoms of a blockage during treatment, tell your doctor or nurse immediately. These include:

- shortness of breath
- difficulty breathing
- cough
- chest discomfort
- fast heart rate
- bluish colour around the mouth, lips or fingernails due to low blood oxygen levels.

In patients with severe or critical acute decompensations, with very high levels of leucine in the blood, Maapliv intravenous might need to be administered in concomitance with haemodialysis or haemofiltration.

The clinical studies focused primarily on leucine levels. The impact on symptom improvement or other aspects of clinical status is unknown.

There is limited information on the repeated administration of the intravenous BCAA- free formula.

Other medicines and Maapliv

Tell your doctor if you are taking, have recently taken or might take any other medicines. Amino acid solutions may precipitate acute folate deficiency and folic acid should be given daily.

Pregnancy, breast-feeding and fertility

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before you are given this medicine.

There are no adequate data concerning the use of Maapliv in pregnant or breast-feeding women.

If you are pregnant, you will receive this medicine only if your doctor considers it absolutely necessary for your recovery. Maapliv should only be given to pregnant women after careful consideration.

At therapeutic doses of Maapliv no effects on the breastfed newborns/infants are anticipated. Nevertheless, Maapliv should only be given to breast-feeding women after careful consideration.

Driving and using machines

Maapliv does not affect your ability to drive or use machines.

3. How to use Maapliv

Maapliv will be given as an infusion (drip) into a vein.

The dose of Maapliv will be adjusted according to your ability to process amino acids, age, weight and nutritional needs.

The recommended dose is between 39 and 58 mL/kg/24h for newborn, infant up to 2 years old and between 19 to 39 mL/kg/24h for children, adolescents and adults.

Keep the bottle protected from light during administration.

If you use more Maapliv than you should

It is very unlikely that you will receive more of this medicine in your infusion than you should, as a doctor or nurse will monitor your treatment.

The effects of an overdose may include symptoms of fluid overload/retention, electrolytic disturbances and acute pulmonary oedema; symptoms of amino acid overdose with shivering, vomiting, headache, nausea, hyperammonaemia (too much ammonia in your blood) and increased loss of amino acids in the kidneys.

In case of overdose, infusion should be stopped immediately and may be resumed with a reduced dose or slower infusion rate.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. The frequency of these adverse reactions is “uncommon” (may affect up to 1 in 100 people).

Serious side effects

- Allergic (anaphylactic, anaphylactoid) reactions. Hypersensitivity. Symptoms may include fever or chills, shivering, excessive sweating, skin rashes, oedema of the face or the eyelids, breathing difficulties, abnormally high heart rate, abnormally low or high blood pressure. If such signs of an allergic reaction occur, the infusion should be stopped immediately.
- Metabolic/nutritional disorders with consequential hyperammonaemia. If hyperammonaemia occurs, infusion should be stopped immediately with specific treatment to be initiated by the treating physician.
- Renal and urinary disorders with consequential azotaemia.
- Formation of blood clots that block blood vessels in the lungs (pulmonary thromboembolism) or veins (venous thromboembolism). This can cause chest pain, breathlessness and fainting. If such signs occur, the infusion should be stopped, and medical evaluation initiated.

Other side effects

- Abnormal blood test for liver function impairment. Blood bilirubin and hepatic enzymes might be increased; and cholecystitis and cholelithiasis might occur.
- Inflammation of the gall bladder, gallstones and problems with bile flow.
- Vein inflammation at infusion site, venous irritation, pain, warmth, swelling and vein duct induration, might occur

If you notice any changes in the way you feel during or after the treatment, tell your healthcare professional or another member of your medical team immediately.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in [Appendix V](#). By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Maapliv

Keep this medicine out of the sight and reach of children.

Store in the original package in order to protect from light.

Do not refrigerate or freeze.

Do not use this medicine after the expiry date, which is stated on the carton and the bottle after EXP. The expiry date refers to the last day of that month.

Do not use this medicine if the bottle is leaking or if you notice particles in the solution.

Do not throw away any medicines via wastewater. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Maapliv contains

- The active substances are L-alanine, L-arginine, L-aspartic acid, L-cysteine hydrochloride monohydrate, L-glutamic acid, Glycine, L-histidine, L-lysine monohydrate, L-methionine, L-phenylalanine, L-proline, L-serine, Taurine, L-threonine, L-tryptophan, L-tyrosine.
- The other ingredients are acetic acid or sodium hydroxide (for pH adjustment) and water for injections.

What Maapliv looks like and contents of the pack

Maapliv is a solution for infusion available in 500 ml colourless glass bottles. Each bottle is packed in a carton.

Clear solution free of particles.

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This leaflet was last revised in.

This medicine has been authorised under ‘exceptional circumstances’.

This means that because of the rarity of the disease it has been impossible to get complete information on this medicine.

The European Medicines Agency will review any new information on this medicine every year and this leaflet will be updated as necessary.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency website: <https://www.ema.europa.eu>. There are also links to other websites about rare diseases and treatments. This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

Annex IV

Conclusions on the granting of the marketing authorisation under exceptional circumstances

Conclusions presented by the European Medicines Agency on:

- **Marketing authorisation under exceptional circumstances**

The CHMP having considered the application is of the opinion that the risk-benefit balance is favourable to recommend the granting of the marketing authorisation under exceptional circumstances as further explained in the European Public Assessment Report.