



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Public summary of opinion on orphan designation

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 the treatment of maple syrup urine disease

On 26 October 2018, orphan designation (EU/3/18/2076) was granted by the European Commission to Orphan Europe SARL, France, for 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 the treatment of maple syrup urine disease.

What is maple syrup urine disease?

Maple syrup urine disease is an inherited disorder in which patients are unable to break down 'branched chain amino acids' or BCAAs which are found in some proteins. As a result, BCAAs build up to toxic levels in the body, particularly in the brain where they can lead to brain damage.

The most severe forms of the disease are present at birth and symptoms include delayed development, behavioural problems and learning disability. Infections or other illness, stresses such as surgery or excess dietary protein may induce severe attacks leading to seizures (fits), swelling and fluid build-up in the brain and coma.

Maple syrup urine disease is a long-term debilitating and life-threatening disorder due to its effects on normal development and damage to the brain.

What is the estimated number of patients affected by the condition?

At the time of designation, maple syrup urine disease affected less than 0.1 in 10,000 people in the European Union (EU). This was equivalent to a total of fewer than 5,000 people*, and is below the ceiling for orphan designation, which is 5 people in 10,000. This is based on the information provided by the sponsor and the knowledge of the Committee for Orphan Medicinal Products (COMP).

¹ Correction active substance.

*Disclaimer: For the purpose of the designation, the number of patients affected by the condition is estimated and assessed on the basis of data from the European Union (EU 28), Norway, Iceland and Liechtenstein. This represents a population of 517,400,000 (Eurostat 2018).



What treatments are available?

At the time of designation, no suitable treatments were authorised in the EU for maple syrup urine disease. Patients were managed with strict diets to control the amount of BCAAs taken in from proteins. Some forms of the disorder also responded to B vitamin supplements.

Some patients needed to be treated in hospital to be fed via a tube or drip with BCAA-free solutions, or procedures to filter BCAAs directly from the blood. Some patients may be suitable for liver transplantation, which restores the ability to break down BCAAs.

How is this medicine expected to work?

The medicine consists of a solution of amino acids (substances that make up proteins) but does not contain any BCAAs. The amino acids are to be given by infusion (drip) into a vein to replace other sources of amino acids. The amino acids are expected to be used by the body to make proteins together with excess BCAAs that have built up because of the disease. This is expected to reduce the level of BCAAs in the body, thereby controlling symptoms of the disease.

What is the stage of development of this medicine?

At the time of submission of the application for orphan designation, clinical trials with the medicine in patients with maple syrup urine disease were ongoing.

At the time of submission, the medicine was not authorised anywhere in the EU for maple syrup urine disease or designated as an orphan medicinal product elsewhere for this condition.

In accordance with Regulation (EC) No 141/2000 of 16 December 1999, the COMP adopted a positive opinion on 13 September 2018 recommending the granting of this designation.

Opinions on orphan medicinal product designations are based on the following three criteria:

- the seriousness of the condition;
- the existence of alternative methods of diagnosis, prevention or treatment;
- either the rarity of the condition (affecting not more than 5 in 10,000 people in the EU) or insufficient returns on investment.

Designated orphan medicinal products are products that are still under investigation and are considered for orphan designation on the basis of potential activity. An orphan designation is not a marketing authorisation. As a consequence, demonstration of quality, safety and efficacy is necessary before a product can be granted a marketing authorisation.

For more information

Sponsor's contact details:

Contact details of the current sponsor for this orphan designation can be found on EMA website, on the medicine's [rare disease designations page](#).

For contact details of patients' organisations whose activities are targeted at rare diseases see:

- [Orphanet](#), a database containing information on rare diseases, which includes a directory of patients' organisations registered in Europe;
- [European Organisation for Rare Diseases \(EURORDIS\)](#), a non-governmental alliance of patient organisations and individuals active in the field of rare diseases.

Translations of the active ingredient and indication in all official EU languages², Norwegian and Icelandic

Language	Active ingredient	Indication
English	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
Bulgarian	Глицин, L-аланин, L-аргинин, L-аспарагинова киселина, L-цистеин, L-глутаминова киселина, L-хистидин, L-лизин монохидрат, L-метионин, L-фенилаланин, L-пролин, L-серин, L-треонин, L-триптофан, L-тирозин, таурин	Лечение на болестта на урина като кленов сироп
Croatian	Glicin, L-alanin, L-arginin, L-asparaginska kiselina, L-cistein, L-glutaminska kiselina, L-histidin, L-lizin monohidrat, L-metionin, L-fenilalanin, L-prolin, L-lizin, L-alanin, L-alanin, L-cistein, -serin, L-treonin, L-triptofan, L-tirozin, taurine	Liječenje bolesti s mirisom urina na javorov sirup
Czech	Glycin, L-alanin, L-arginin, L-asparágová kyselina, L-cystein, L-glutamová kyselina, L-histidin, L-lysin monohydrát, L-methionin, L-fenylalanin, L-prolin, L-serin, L-threonin, L-tryptofan, L-tyrosin, taurin	Léčba leucinózy
Danish	Glycin, L-alanin, L-arginin, L-asparaginsyre, L-cystein, L-glutaminsyre, L-histidin, L-lysine monohydrat, L-methionin, L-phenylalanin, L-prolin, L-serin, L-threonin, L-tryptofan, L-tyrosin, taurin	Behandling af ahornsirup-urin sygdom
Dutch	Glycine, L-alanine, L-arginine, L-asparaginezuur, L-cysteïne, L-glutaminezuur, L-histidine, L-lysine monohydraat, L-methionine, L-fenylalanine, L-proline, L-serine, L-threonine, L-tryptofaan, L-tyrosine, taurine	Behandeling van ahornstroopziekte (Maple syrup urineziekte)
Estonian	Glütsiin, L-alaniin, L-arginiin, L- aspartaamhape, L-tsüsteiin, L-glutamiinhape, L-histidiin, L-lüsiinmonohüdraat, L-metioniin, L-fenüülalaniin, L-proliin, L-seriin, L-treoniin, L-trüptofaan, L-türosiin, tauriin	Vahtrasiirupi tõve ravi
Finnish	Glysiini, L-alaniini, L-arginiini, L-asparagiinihappo, L-kysteiini, L-glutamiinihappo, L-histidiini, L-lysiinimonohydraatti, L-metioniini, L-fenyyilalaniini, L-proliini, L-seriini, L-treoniini, L-tryptofaani, L-tyroosiini, tauriini	Vaahterasiirappitaudin hoitoon

² At the time of designation

Language	Active ingredient	Indication
French	Glycine, L-alanine, L-arginine, acide L-aspartique, L-cystéine, acide L-glutamique, L-histidine, L-lysine monohydrate, L-méthionine, L-phénylalanine, L-proline, L-sérine, L-thréonine, L-tryptophane, L-tyrosine, taurine	Traitement de la leucinose
German	Glycin, L-alanin, L-arginin, L-asparaginsäure, L-cystein, L-glutaminsäure, L-histidin, L-lysin monohydrat, L-methionin, L-phenylalanin, L-prolin, L-serin, L-threonin, L-tryptophan, L-tyrosin, taurin	Behandlung der Ahornsirupkrankheit
Greek	Γλυκίνη, L-αλανίνη, L-αργινίνη, L-ασπαρτικό οξύ, L-κυστεΐνη, L-γλουταμικό οξύ, L-ιστιδίνη, μονοϋδρική L-λυσίνη, L-μεθειονίνη, L-φαινυλαλανίνη, L-προλίνη, L-σερίνη, L-θρεονίνη, L-τρυπτοφάνη, L-τυροσίνη, ταυρίνη	Θεραπεία της νόσου ούρων με οσμή σφενδάμου
Hungarian	Glicin, L-alanin, L-arginin, L-aszpartámsav, L-cisztein, L-glutaminsav, L-hisztidin, L-lizin-monohidrát, L-metionin, L-fenilalanin, L-prolin, L-szerin, L-treonin, L-triptofán, L-tirozin, taurin	Jávorfaszirup-betegség kezelése
Italian	Glicina, L-alanina, L-arginina, L-acido aspartico, L-cisteina, L-acido glutammico, L-istidina, L-lisina monoidrato, L-metionina, L-fenilalanina, L-prolina, L-serina, L-treonina, L-triptofano, L-tirosina, taurina	Trattamento della malattia delle urine a sciroppo d'acero
Latvian	Glicīns, L-alanīns, L-arginīns, L-asparagīnskābe, L-cisteīns, L-glutamīnskābe, L-histidīns, L-lizīna monohidrāts, L-metionīns, L-fenilalanīns, L-prolīns, L-serīns, L-treonīns, L-triptofāns, L-tirozīns, taurīns	Sazarotās ķēdes ketoacidūrijas ("kļavu sīrupa urīna" slimības) ārstēšanai
Lithuanian	Glicinas, L-alaninas, L-argininas, L-asparto rūgštis, L-cisteinas, L-glutamo rūgštis, L-histidinas, L-lizino monohidratas, L-metioninas, L-fenilalaninas, L-prolinas, L-serinas, L-treoninas, L-triptofanas, L-tirozinas, taurinas	Klevų sirupo šlapime ligos gydymas
Maltese	Glicina, L-alanina, L-arginina, L-aspartic acid, L-cisteina, L-glutamic acid, L-istidina, L-monodirat ta' liżina, L-metijonina, L-phenylalanine, L-prolina, L-serina, L-treonina, L-tryptophan, L-tirożina, tawrina	Kura ta' marda tal-awrina maple syrup
Polish	Glicyna, L-alanina, L-arginina, L-kwas asparginowy, L-cysteina, L-kwas glutaminowy, L-histydyna, L-lizyna monohydrat, L-metionina, L-feniloalanina, L-prolina, L-seryna, L-treonina, L-tryptofan, L-tyrozyna, tauryna	Leczenie choroby syropu klonowego

Language	Active ingredient	Indication
Portuguese	Glicina, L-alanina, L-arginina, ácido L-aspartico, L-cisteína, ácido L-glutâmico, L-histidina, L-lisina monohidrato, L-metionina, L-fenilalanina, L-prolina, L-serina, L-treonina, L-triptofano, L-tirosina, taurina	Tratamento da leucínose
Romanian	Glicină, L-alanină, L-arginină, acid L-aspartic, L-cisteină, acid L-glutamic, L-histidină, monohidrat de L-lizină, L-metionină, L-fenilalanină, L-prolină, L-serină, L-treonină, L-triptofan, L-tirozină, taurină	Tratarea bolii urinei cu miros de sirop de arțar
Slovak	Glycín, L-alanín, L-arginín, L-asparágová kyselina, L-cysteín, L-glutámová kyselina, L-histidín, L-lyzín monohydrát, L-metionín, L-fenylalanín, L-prolín, L-serín, L-treonín, L-tryptofán, L-tyrozín, taurín	Liečba choroby javorového sirupu
Slovenian	Glicin, L-alanin, L-arginin, L-asparaginska kislina, L-cistein, , L-glutaminska kislina, L-histidin, L-lizin monohidrat, L-metionin, L-fenilalanin, L-prolin, L-serin, L-treonin, L-triptofan, L-tirozin, taurin	Zdravljenje bolezni javorjevega sirupa
Spanish	Glicina, L-alanina, L-arginina, ácido L-aspartico, L-cisteína, ácido L-glutámico, L-histidina, L-lisina monohidrato, L-metionina, L-fenilalanina, L-prolina, L-serina, L-treonina, L-triptófano, L-tirosina, taurina	Tratamiento de la enfermedad de la orina con olor a jarabe de arce
Swedish	Glycin, L-alanin, L-arginin, L-asparaginsyra, L-cystein, L-glutaminsyra, L-histidin, L-lysinmonohydrat, L-metionin, L-fenylalanin, L-prolin, L-serin, L-treonin, L-tryptofan, L-tyrosin, taurin	Behandling av maple syrup urine disease
Norwegian	Glycin, L-alanin, L-arginin, L-asparaginsyre, L-cystein, L-glutaminsyre, L-histidin, L-lysinmonohydrat, L-metionin, L-fenylalanin, L-prolin, L-serin, L-treonin, L-tryptofan, L-tyrosin, taurin	Behandling av Maple Syrup Urine Disease
Icelandic	Glýsín, L-alanín, L-arginín, L-asparssýra, L-systeín, L-glútamínsýra, L-histidín, L-lýsín einhýdrat, L-metíónín, L-fenýlalanín, L-prólín, L-serín, L-treónín, L-trýptófan, L-týrósín, tárín	Meðferð við hlynsýrópssýki