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Public summary of opinion on orphan designation

Modified mRNA encoding human methylmalonyl-coenzyme A mutase encapsulated into lipid nanoparticles for the treatment of methylmalonic acidaemia

On 25 May 2018, orphan designation (EU/3/18/2025) was granted by the European Commission to Pharma Gateway AB, Sweden, for modified mRNA encoding human methylmalonyl-coenzyme A mutase encapsulated into lipid nanoparticles (also known as mRNA-3704) for the treatment of methylmalonic acidaemia.

What is methylmalonic acidaemia?

Methylmalonic acidaemia is an inherited condition in which the body does not process proteins and fats properly. It is caused by mutations (changes) in certain genes responsible for producing a protein called methylmalonyl-CoA mutase.

The condition usually appears in early infancy, with the patient having high levels of acid and ammonia in the blood. Symptoms include poor feeding, vomiting, weak muscle tone causing floppiness, lethargy (lack of energy) and problems with the brain.

Methylmalonic acidaemia is a long-term debilitating condition and is life threatening due to complications affecting the nervous system, gut and blood.

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

At the time of designation, methylmalonic acidaemia affected less than 0.4 in 10,000 people in the European Union (EU). This was equivalent to a total of fewer than 21,000 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).

*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).

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What treatments are available?

At the time of the orphan designation, Carbaglu was authorised in the EU for treating high levels of ammonia that occur in patients with methylmalonic acidaemia. Other medicines were used to reduce production of acid in the gut. Patients could also avoid further build-up of ammonia in the blood by eating a low-protein diet.

The sponsor has provided sufficient information to show that the medicine might be of significant benefit for patients with methylmalonic acidaemia, with laboratory data indicating that it could reduce the build-up of acid and improve survival.

This assumption will need to be confirmed at the time of marketing authorisation, in order to maintain the orphan status.

How is this medicine expected to work?

In patients with methylmalonic acidaemia, the methylmalonyl-CoA mutase protein, which is involved in reactions to break down proteins and fats, does not work properly.

This medicine is made of genetic material contained in fatty particles. When injected into the patient, it is expected that the fatty particles deliver the genetic material to liver cells, making them able to produce functional methylmalonyl-CoA mutase. This is expected to reduce patients' symptoms.

What is the stage of development of this medicine?

The effects of the medicine have been evaluated in experimental models.

At the time of submission of the application for orphan designation, no clinical trials with the medicine in patients with methylmalonic acidaemia had been started.

At the time of submission, the medicine was not authorised anywhere in the EU for methylmalonic acidaemia 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 19 April 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 languages[1], Norwegian and Icelandic

Language	Active ingredient	Indication
English	Modified mRNA encoding human methylmalonyl-coenzyme A mutase encapsulated into lipid nanoparticles	Treatment of methylmalonic acidaemia
Bulgarian	Модифицирана иРНК, кодираща човешката метилмалонил-коензим А мутаза, капсулирана в липидни наночастици	Лечение на метилмалонова ацидемия
Croatian	Modificirana mRNA koja kodira ljudsku mutazu metilmalonil-koenzima A, inkapsulirana u lipidnim nanočesticama	Liječenje metilmalonične acidemije
Czech	Modifikovaná mRNA, která kóduje lidskou methylmalonyl-koenzym A mutázu zapouzdřenou do lipidových nanočástic	Léčba izolované methylmalonové acidémie
Danish	Modificeret mRNA, kodende for human methylmalonyl-coenzym A-mutase, indkapslet i lipidnanopartikler	Behandling af methylmalonacidæmi
Dutch	Gemodificeerd mRNA dat codeert voor humane methylmalonyl-co-enzym-A-mutase ingekapseld in lipide nanodeeltjes	Behandeling van methylmalonacidemie
Estonian	Lipiidsetesse nanoosakestesse kapseldatud, inimese metüülmalonüül-koensüüm A mutaasi kodeeriv modifitseeritud mRNA	Metüülmaloonhappe atsideemia ravi
Finnish	Lipidinanohiukkasiin kapseloitu ihmisen metyylimalonyylikoentsyymi-A-mutaasin koodaajana toimiva muunneltu mRNA	Metyylimalonihappovirtsaisuuden hoito
French	mARN codant l'enzyme méthylmalonyl-coA mutase humaine, encapsulé dans des nanoparticules lipidiques	Traitement de l'acidémie méthylmalonique
German	In Lipid-Nanopartikel verkapselte mRNA , die die humane Methylmalonyl-Coenzym-A-Mutase kodiert	Behandlung der Methylmalonazidämie
Greek	Τροποποιημένο mRNA που κωδικοποιεί τη μουτάση του ανθρώπινου μεθυλομαλονυλο-συνενζύμου Α ενθυλακωμένο σε νανοσωματίδια λιπιδίων	Θεραπεία της μεθυλμαλονικής οξυαιμίας
Hungarian	Lipid nanorészecskékbe zárt humán metil-malonil-koenzim-A-mutázt kódoló módosított mRNS	A metil-malonsavas acidémia kezelése
Italian	mRNA modificato, incapsulato in nanoparticelle lipidiche, codificante la metilmalonil-coenzima A mutasi umana	Trattamento dell'acidemia metilmalonica
Latvian	Lipīdu nanodaļiņās iekapsulēta modificēta mRNS, kas kodē cilvēka metilmalonilkoenzīma A mutāzi	Metilmalonacidēmijas ārstēšana
Lithuanian	Modifikuota iRNR, koduojanti žmogaus metilmalonil-koenzimo A mutazę, inkapsuliuota į lipidų nanodaleles	Metilmalono acidemijos gydymas

[1] At the time of designation

Language	Active ingredient	Indication
Maltese	mRNA modifikat li jikkodifika metilmalonil-koenzima A mutaži uman, inkapsulat f'nanopartiċelli tal-lipidi	Trattament ta' aċidemija metilmaloniku
Polish	Zmodyfikowany mRNA kodujący ludzką mutazę metylomalonylo-koenzymu A zamknięty w nanocząsteczkach lipidowych	Leczenie kwasicy metylmalonowej
Portuguese	ARNm modificado que codifica a coenzima metilmalonil A mutase humana encapsulada em nanopartículas lipídicas	Tratamento da acidemia metilmalónica
Romanian	Acid ribonucleic mesager modificat care codifică metilmalonil-coenzima A mutază umană încapsulat în nanoparticule lipidice	Tratamentul acidemiei metilmalonice
Slovak	Modifikovaná mRNA kódujúc ľudskú mutázu metylmalonyl-koenzýmu A zasadená do lipidových nanočastíc	Liečba metylmalonylovej acidémie
Slovenian	Modificirana mRNA, ki kodira humano metilmalonil-CoA mutazo, inkapsulirana v lipidne nanodelce	Zdravljenje metilmalonske acidemije
Spanish	ARNm modificado que codifica la metilmalonil coenzima A mutasa encapsulado en nanopartículas lipídicas	Tratamiento de la acidemina metilmalónica
Swedish	Modifierat mRNA som kodar för humant metylmalonyl-CoA-mutas inkapslat i lipida nanopartiklar	Behandling av metylmalonisk acidemi
Norwegian	Modifisert mRNA som koder for humant metylmalonyl-CoA-mutase innkapslet i lipide nanopartikler	Behandling av metylmalonsyreemi
Icelandic	Breytt mótandi RNA sem felur í sér manna metýlmalónýl kóensím-A mútasa hjúpaðan fitunanóögnum	Meðferð við metýlmalón blóðsýringu