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Public summary of opinion on orphan designation

Modified messenger ribonucleic acid encoding human propionyl-coenzyme A carboxylase alpha and beta subunits encapsulated into lipid nanoparticle for the treatment of propionic acidaemia

On 24 April 2019, orphan designation (EU/3/19/2156) was granted by the European Commission to Pharma Gateway AB, Sweden, for modified messenger ribonucleic acid encoding human propionyl-coenzyme A carboxylase alpha and beta subunits encapsulated into lipid nanoparticle (also known as mRNA-3927) for the treatment of propionic acidaemia.

What is propionic acidaemia?

Propionic acidaemia is an inherited disease in which the body does not break down amino acids and fats properly. It is caused by mutations (changes) in genes responsible for producing an enzyme called propionyl CoA carboxylase. As a result, acids and ammonia build up in the blood and body tissues.

The condition usually appears shortly after birth and causes symptoms such as poor feeding, vomiting, reduced muscle strength, lack of energy, an enlarged heart and encephalopathy (a brain disorder).

Propionic acidaemia is a long-term debilitating and life-threatening disease because it can lead to fits, coma and heart failure.

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

At the time of designation, propionic acidaemia affected approximately 0.04 in 10,000 people in the European Union (EU). This was equivalent to a total of around 2,000 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 518,400,000 (Eurostat 2019).

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What treatments are available?

At the time of the orphan designation, Carbaglu was authorised in the EU for reducing high levels of ammonia in the blood of patients with propionic acidaemia. Other medicines were used to reduce production of acid in the gut. Patients were also advised to 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 propionic acidaemia, with laboratory data indicating that it could reduce the build-up of ammonia and reduce heart mass. 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 propionic acidaemia, the enzyme propionyl CoA carboxylase, which is involved in breaking down amino acids and fatty acids, 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 into liver cells, making them able to produce working propionyl CoA carboxylase. 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 propionic acidaemia had been started.

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

In accordance with Regulation (EC) No 141/2000, the COMP adopted a positive opinion on 21 March 2019, 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.

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 messenger ribonucleic acid encoding human propionyl-coenzyme A carboxylase alpha and beta subunits encapsulated into lipid nanoparticle	Treatment of propionic acidaemia
Bulgarian	Модифицирана информационна рибонуклеинова киселина, кодираща алфа- и бета-субединиците на човешки пропионил-коензим А карбоксилаза, капсулирана в липидни наночастици	Лечение на пропионова ацидемия
Croatian	Modificirana glasnička ribonukleinska kiselina koja kodira alfa i beta podjedinice humane propionil-koenzim A karboksilaze enkapsulirana u lipidne nanočestice	Liječenje propionske acidemije
Czech	Modifikovaná messengerová ribonukleová kyselina kódující podjednotky alfa a beta karboxylázy lidského propionylkoenzymu A karboxylázy enkapsulované do lipidových nanočástic	Léčba propionové acidémie
Danish	Modificeret messenger-ribonukleinsyre, kodende for alfa- og beta-subunits af human propionyl-coenzym A-carboxylase, indkapslet i lipidnanopartikler	Behandling af propionsyreæmi
Dutch	Gemodificeerd messenger ribonucleïnezuur dat codeert voor alfa- en bèta-subeenheden van humaan propionyl-co-enzym A-carboxylase ingekapseld in lipide nanodeeltjes	Behandeling van propionische acidemie
Estonian	Lipiidsetesse nanoosakestesse kapseldatud modifitseeritud mRNA, mis kodeerib inimese propionüülkoensüüm A karboksülaasi alfa- ja beeta alaühikuid	Propioon-atsideemia ravi
Finnish	Modifioitu lähetti-RNA, joka koodaa ihmisen propionyylikoentsyymi-A-karboksylaasin alfa –ja beeta alayksiköitä kapseloituina lipidinanopartikkeleihin	Propionihappoverisyyden hoito

[1] At the time of designation

Language	Active ingredient	Indication
French	Acide ribonucléique messager modifié codant pour les sous-unités alpha et bêta de la propionyl-coenzyme A carboxylase humaine encapsulée dans des nanoparticules lipidiques	Traitement de l'acidémie propionique
German	Modifizierte Boten-Ribonukleinsäure, die für menschliche Propionyl-Coenzym-A-Carboxylase Untereinheiten alpha und beta kodiert, und in Lipid-Nanopartikel eingekapselt ist	Behandlung der Propionazidämie
Greek	Τροποποιημένο αγγελιοφόρο ριβονουκλεϊκό οξύ που κωδικοποιεί τις υπομονάδες άλφα και βήτα καρβοξυλάσης του ανθρώπινου προπιονυλο-συνενζύμου Α ενθυλακωμένο σε νανοσωματίδια λιπιδίων	Θεραπεία προπιονικής οξυαιμίας
Hungarian	Lipid nanorészecskékbe enkapszulált módosított messenger ribonukleinsav, amely a humán propionil-koenzim A karboxiláz alfa és béta alegységeit kódolja	Propionsav-acidaemia kezelése
Italian	Acido ribonucleico messaggero modificato che codifica le subunità alfa e beta della propionil-coenzima A carbossilasi umana, incapsulato in nanoparticelle lipidiche	Trattamento dell'acidemia propionica
Latvian	Modificēta matrices ribonukleīnskābe, kas kodē cilvēka propionilkoenzīma A karboksilāzes alfa un beta subvienības un kas iekapsulēta lipīdu nanodaļiņās	Propionacidēmijas ārstēšana
Lithuanian	Modifikuota informacinė ribonukleino rūgštis, koduojanti žmogaus propionil-KoA karboksilazės alfa ir beta subvienetus, inkapsuliuotus į lipidų nanodaleles	Propiono acidemijos gydymas
Maltese	Aċidu ribonukleiku messaġġier modifikat li jikkodifika propjonil-koenzima A tal-bniedem karbossilaży alfa u sottounitajiet beta inkapsulati f'nanopartikula lipidika	Kura ta' l-aċidemija propijonika
Polish	Zmodyfikowany matrycowy kwas rybonukleinowy kodujący ludzką karboksylazę propionylo-CoA (podjednostki alfa i beta) zamknięty w nanocząstkach lipidowych	Leczenie acydemii propionowej
Portuguese	Ácido ribonucleico mensageiro modificado que codifica as subunidades alfa e beta da propionil-coenzima A carboxilase humana, encapsulado em nanopartículas lipídicas	Tratamento da acidémia propiónica

Language	Active ingredient	Indication
Romanian	Acid ribonucleic mesager modificat care codifică subunitățile alfa și beta ale propionil-coenzima A-carboxilazei umane, încapsulat in nanoparticule lipidice	Tratamentul acidemiei propionice
Slovak	Modifikovaná mediátorová ribonukleová kyselina kódujúca alfa a beta podjednotky propionyl-koenzým A karboxylázy zapuzdrená v lipidových nanočasticiach	Liečba propiónovej acidémie
Slovenian	Modificirana messenger ribonukleinska kislina, ki kodira podenoti α in β humane propionil CoA karboksilaze, inkapsulirana v lipidne nanodelce	Zdravljenje acidemije zaradi propionske kisline
Spanish	Ácido ribonucleico mensajero modificado que codifica la propionil-coenzima A carbosxilasa subunidades α y β encapsulada en nanopartículas lipídicas	Tratamiento de la acidemia propiónica
Swedish	Modifierad budbärarribonukleinsyra som kodar för alfa- och beta subenheter av humant propionyl CoA dekarboxylas inkapslat i lipidnanopartiklar	Behandling av propionisk acidemi
Norwegian	Modifisert budbringer-ribonukleinsyre som koder for alfa- og beta-subenheter av humant propionyl-koenzym A karboksylase innkapslet i lipidnanopartikler	Behandling av propionisk acidemi
Icelandic	Breytt mRNA sem kóðar fyrir alfa- og beta-undireiningum própíónýl-kóensím A karboxýlasa manna, innfellt í fitunanóagnir	Meðferð við própíón blóðsýringu