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EMA/750696/2017

Public summary of opinion on orphan designation

Modified messenger ribonucleic acid encoding human argininosuccinate lyase enzyme encapsulated into lipid nanoparticles for the treatment of argininosuccinic aciduria

On 12 December 2017, orphan designation (EU/3/17/1952) was granted by the European Commission to PhaseRx Ireland, Ltd, Ireland, for modified messenger ribonucleic acid encoding human argininosuccinate lyase enzyme encapsulated into lipid nanoparticles (also known as PRX-ASL) for the treatment of argininosuccinic aciduria.

What is argininosuccinic aciduria?

Argininosuccinic aciduria is one of the inherited disorders known as 'urea-cycle disorders', which cause ammonia to accumulate in the blood. Patients with argininosuccinic aciduria lack argininosuccinate lyase, one of the liver enzymes needed to get rid of excess nitrogen. In the absence of this liver enzyme, excess nitrogen accumulates in the body in the form of ammonia, which can be harmful at high levels, especially to the brain. Symptoms of the disease usually appear in the first few days of life and include lethargy (lack of energy), vomiting, loss of appetite, seizures (fits) and coma.

Argininosuccinic aciduria is a long-term debilitating and life-threatening disease that leads to developmental delay and mental disability and is associated with a high mortality rate.

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

At the time of designation, argininosuccinic aciduria 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).

What treatments are available?

At the time of designation, Ravicti (glycerol phenylbutyrate) was authorised in the EU for the treatment of urea cycle disorders including argininosuccinic aciduria. Sodium benzoate was also used although

*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 515,700,000 (Eurostat 2017).

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not authorised for this condition. Patients were also advised to control their dietary intake of proteins, which are rich in nitrogen, to reduce the amount of ammonia formed in the body.

The sponsor has provided sufficient information to show that the medicine might be of significant benefit for patients with argininosuccinic aciduria because laboratory studies show that the medicine, when used with other products, can help reduce ammonia levels in the blood. 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?

The medicine consists of genetic material (messenger RNA) containing the instructions cells need to make the missing enzyme, argininosuccinate lyase. The genetic material is enclosed in fatty particles to protect it and it is injected with another substance to help it enter liver cells. Once it has entered the cells, it is expected to enable them to produce argininosuccinate lyase and so reduce the symptoms caused by its deficiency.

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 argininosuccinic aciduria had been started.

At the time of submission, the medicine was not authorised anywhere in the EU for argininosuccinic aciduria. Orphan designation of the medicine had been granted in the US for this condition.

In accordance with Regulation (EC) No 141/2000 of 16 December 1999, the COMP adopted a positive opinion on 31 October 2017 recommending the granting of this designation.

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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 messenger ribonucleic acid encoding human argininosuccinate lyase enzyme encapsulated into lipid nanoparticles	Treatment of argininosuccinic aciduria
Bulgarian	Модифицирана информационна рибонуклеинова киселина, кодираща човешки аргининосукцинат лиазен ензим, капсулирана в липидни наночастици	Лечение на аргининосукцининова ацидурия
Croatian	Modificirana glasnička ribonukleinska kiselina koja kodira humani enzim argininosukcinat liaze enkapsuliran u lipidne nanočestice	Liječenje argininosukcinske acidurije
Czech	Modifikovaná messengerová ribonukleová kyselina kódující enzym lidského argininosukcinátu lyasy enkapsulovaný do lipidových nanočástic	Léčba argininosukcinátové acidurie
Danish	Modificeret messenger ribonukleinsyre som koder for humant argininosuccinat lyase enzym indkapslet i lipid nanopartikler	Behandling af argininravsyreuri
Dutch	Gemodificeerd messenger ribonucleïnezuur dat codeert voor humaan argininosuccinaat lyase enzym ingekapseld in lipide nanodeeltjes	Behandeling van argininosuccinic aciduria
Estonian	Modifitseeritud messenger ribonukleiinhape, mis kodeerib inimese arginiinsuktsinaatlüaasi ensüümi, mis on kapseldatud lipiidide nanoosakestele	Argininosuktsiin-atsiduuria ravi
Finnish	Modifioitu lähetti-RNA, joka koodaa ihmisen arginiinisukkinaatti-lyaaasientsyymiä, kapseloituna lipidi nanopartikkeleihin	Argininosukkinaattiasidurian hoito
French	Acide ribonucléique messager modifié codant pour l'enzyme argininosuccinate lyase humaine encapsulée dans les nanoparticules lipidiques	Traitement de l'acidurie argininosuccinique
German	Modifizierte Boten-Ribonukleinsäure, die für menschliches Argininosuccinat-Lyase-Enzym kodiert, und in Lipid-Nanopartikel eingekapselt ist	Behandlung einer Argininosukzinoazidurie
Greek	Τροποποιημένο αγγελιοφόρο ριβονουκλεϊκό οξύ που κωδικοποιεί το ένζυμο της ανθρώπινης αργινινοηλεκτρικής λυάσης ενθυλακωμένο σε νανοσωματίδια λιπιδίων	Θεραπεία της αργινοηλεκτρικής οξυουρίας.
Hungarian	Lipid nanorészecskékbe enkapszulált módosított messenger ribonukleinsav, amely humán arginin-szukcinát-liáz enzimet kódol	Argininoszukcinin anuria kezelésére
Italian	Acido ribonucleico messaggero modificato che codifica l'enzima dell' arginosuccinato liasi umana, incapsulato in nanoparticelle lipidiche	Trattamento dell'aciduria argininosuccinica

[1] At the time of designation

Language	Active ingredient	Indication
Latvian	Modificēta matrices ribonukleīnskābe, kas kodē cilvēka argininosukcinātu liāzes fermentu un kas iekapsulēta lipīdu nanodaļiņās	Arginīna sukcināta acidūrijas ārstēšana
Lithuanian	Modifikuota informacinė ribonukleorūgštis, koduojanti žmogaus argininsukcinato liazės fermentą, įkapsuliuotą į lipidų nanodaleles	Arginino sukcininės acidurijos gydymas
Maltese	Aċidu ribonuklejku messaġġier modifikat li jikkodifika l-enzima tal-argininosuċċinat liażi tal-bniedem inkapsulata f'nanoartikoli lipidi	Kura tal-aċidurja arġininosuċċinika
Polish	Zmodyfikowany matrycowy kwas rybonukleinowy kodujący ludzki enzym laktozy argininosukrylanu zamknięty w nanocząstkach lipidowych	Leczenie acydurii argininobursztynianowej
Portuguese	Ácido ribonucleico mensageiro modificado que codifica a enzima argininosuccinato liase humana encapsulado em nanopartículas lipídicas	Tratamento da acidúria argininosuccínica
Romanian	Acidul ribonucleic mesager modificat care codifică enzima umană argininsuccinat liaza încapsulată în nanoparticule lipidice	Tratamentul aciduriei argininosuccinice
Slovak	Modifikovaná messenger ribonukleová kyselina kódujúca ľudský arginínsukcinát lyázový enzým zapuzdrený do lipidových nanočastíc	Liečba arginínosukcinátovej acidúrie
Slovenian	Modificirana messenger ribonukleinska kislina, ki kodira humani argininosukcinatni lizazni encim, inkapsuliran v lipidne nanodelce	Zdravljenje argininsukcinilne acidurije
Spanish	Ácido ribonucleico mensajero modificado que codifica la enzima argininosuccinato liasa humana encapsulada en nanopartículas lipídicas	Tratamiento de la aciduria argininsuccínica
Swedish	Modifierad budbärarribonukleinsyra som kodar för humant argininosuccinat-lyasenzym inkapslat i lipidnanopartiklar	Behandling av argininbärnstensaciduri
Norwegian	Modifisert messenger ribonukleinsyre som koder for humant argininosuccinat-lyase enzym innkapslet i lipid nanopartikler	Behandling av argininravsyreaciduri
Icelandic	Breyttur sendiboða ríbó kjarnsýru sem kóðar fyrir manna arginínósúkkínat lýasensím sem er innhellt í fituefni	Meðferð á arginínósúksíniksýrumigu