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Committee for Orphan Medicinal Products

# Public summary of opinion on orphan designation

## Modified messenger ribonucleic acid encoding human ornithine transcarbamylase enzyme encapsulated into lipid nanoparticles for the treatment of ornithine transcarbamylase deficiency

On 20 April 2017, orphan designation (EU/3/17/1867) was granted by the European Commission to PhaseRx Ireland, Ltd, Ireland, for modified messenger ribonucleic acid encoding human ornithine transcarbamylase enzyme encapsulated into lipid nanoparticles (also known as PRX-OTC) for the treatment of ornithine transcarbamylase deficiency.

### What is ornithine transcarbamylase deficiency?

Ornithine transcarbamylase deficiency is one of the inherited disorders known as urea-cycle disorders, which cause ammonia to build up in the blood. Patients with ornithine transcarbamylase deficiency lack ornithine transcarbamylase, one of the liver enzymes needed to get rid of excess nitrogen. In the absence of this enzyme, 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 may appear in the first few days of life (particularly in boys) and include lethargy (lack of energy), vomiting, loss of appetite, seizures (fits) and coma, often leading to death. However, the age at which symptoms start is highly variable, particularly in females.

Ornithine transcarbamylase deficiency is a long-term debilitating and life-threatening disease that can alter brain function and is associated with poor overall survival.

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

At the time of designation, ornithine transcarbamylase deficiency affected approximately 0.1 in 10,000 people in the European Union (EU). This was equivalent to a total of around 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).

[*]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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## What treatments are available?

At the time of designation, glycerol phenylbutyrate (Ravicti) and sodium phenylbutyrate (Ammonaps, Pheburane) were authorised in the EU for the treatment of some urea-cycle disorders, including ornithine transcarbamylase deficiency. In addition, patients were advised to control their dietary intake of proteins, which are rich in nitrogen, to reduce the amount of ammonia formed in the body. Liver transplantation was used to manage the condition in some people.

The sponsor has provided sufficient information to show that the medicine might be of significant benefit for patients with ornithine transcarbamylase deficiency because laboratory studies show that it reduces ammonia in the blood and improves orotic aciduria, a sign of urea-cycle disorders. 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 that liver cells need to make the missing enzyme, ornithine transcarbamylase. The genetic material is enclosed in fatty particles to protect it and it is injected with another substance to help it enter liver cells. Giving the medicine by infusion (drip) into a vein every 7 to 14 days is expected to enable liver cells to produce ornithine transcarbamylase 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 ornithine transcarbamylase deficiency had been started.

At the time of submission, the medicine was not authorised anywhere in the EU for ornithine transcarbamylase deficiency. Orphan designation of the medicine had been granted in United States for ornithine transcarbamylase deficiency.

In accordance with Regulation (EC) No 141/2000 of 16 December 1999, the COMP adopted a positive opinion on 15 March 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 ornithine transcarbamylase enzyme encapsulated into lipid nanoparticles | Treatment of ornithine transcarbamylase deficiency |
| Bulgarian | Модифицирана информационна рибонуклеинова киселина кодираща човешката орнитин транскарбамилаза, капсулирана в липидни наночастици | Лечение на дефицит на орнитин транскарбамилаза |
| Croatian | Modificirani glasnik ribonukleinske kiseline koji kodira enzim ljudske ornitin transkarbamilaze zatvoren u lipidne nanočestice | Liječenje nedostatka ornitin-transkarbamilaze |
| Czech | Modifikovaná messengerová ribonukleová kyselina kodující lidský enzym ornitin-karbamoyltransferázy zapouzdřený do lipidových nanočástic | Léčba nedostatku transkarbamylázy ornithine |
| Danish | Modificeret messenger ribonukleinsyre, der koder for human ornithintranscarbamylase enzym indkapslet i lipidnanopartikler | Behandling af ornithin transcarbamylase defect |
| Dutch | Gemodificeerde messenger ribonucleïnezuur dat codeert voor humaan ornithinetranscarbamylase enzym ingekapseld in lipide nanodeeltjes | Behandeling van ornithine transcarbamylase deficiëntie |
| Estonian | Lipiidsetesse nanoosakestesse kapseldatud inimese ornitiintranskarbamülaasi ensüümi kodeeriv modifitseeritud messenger ribonukleiinhape | Ornitiintranskarbamülaasi puudulikkuse ravi |
| Finnish | Modifioitu lähetti-RNA, joka koodaa ihmisen ornitiinitranskarbamylaasi entsyymiä kapseloituna lipidinanohiukkasiin | Ornitiinitranskarbamylaasin puutoksen hoito |
| French | Acide ribonucléique messager modifié codant l'enzyme ornithine transcarbamylase humaine encapsulée dans des nanoparticules lipidiques | Traitement du déficit en ornithine transcarbamylase |
| German | Modifizierte Boten-Ribonukleinsäure, die für humanes Ornithintranscarbamylase-Enzym kodiert, das in Lipid-Nanopartikel eingekapselt ist | Behandlung des Ornithintranscarbamylase-Mangels |
| Greek | Τροποποιημένο αγγελιοφόρο ριβονουκλεϊκό οξύ που κωδικοποιεί το ανθρώπινο ένζυμο ορνιθίνης τρανσκαρβαμυλάσης, ενθυλακωμένο σε λιπιδικά νανοσωματίδια | Θεραπεία της έλλειψης της τρανσκαρβαμυλάσης της ορνιθίνης |

[1] At the time of designation

| Language | Active ingredient | Indication |
|---|---|---|
| Hungarian | Lipid nanorészecskékbe enkapszulált humán ornitin transzkarbamiláz enzimet kódoló módosított messenger ribonukleinsav | Ornitin transzkarbamiláz hiány kezelése |
| Italian | Acido ribonucleico messaggero modificato, incapsulato in nanoparticelle lipidiche, che codifica per l' enzima ornitina transcarbamilasi umana | Trattamento del deficit di ornitina-transcarbamilasi |
| Latvian | Lipīdu nanodaļiņās iekapsulēta, modificēta matrices ribonukleīnskābe, kas kodē cilvēka ornitīna transkarbamilāzes enzīmu | Ornitīna transkarbamilāzes nepietiekamības ārstēšana |
| Lithuanian | Modifikuota informacinė ribonukleininė rūgštis, koduojanti žmogaus ornitino transkarbomilazės fermentą, įterptą į lipidų nanodaleles | Ornitintranskarbamilazės stokos gydymas |
| Maltese | Aċidu ribonuklejku messaġġier modifikat b'ikkowdjar tal-enzima tat-transkarbamilaži tal-ornitina umana inkapsulata f'nanopartiċelli lipidi | Kura ta' defiċjenza ta' l-Ornithine Transcarbamylase |
| Polish | Zawarty w nanocząstkach lipidowych, zmodyfikowany matrycowy kwas rybonukleinowy kodujący enzym ludzkiej a transkarbamylazy ornityny | Leczenie pacjentów z niedoborem transkarbamylazy ornitynowej |
| Portuguese | Ácido ribonucleico mensageiro modificado que codifica a enzima ornitina transcarbamilase humana encapsulada em nanopartículas lipídicas | Tratamento da deficiência de ornitina-transcarbamilase |
| Romanian | Acid ribonucleic mesager modificat incapsulat in nanoparticule lipidice ce codifică enzima ornitin transcarbamilaza umană | Tratamentul deficitului de ornitin-transcarbamilază |
| Slovak | Modifikovaná messenger ribonukleová kyselina kódujúca ľudský enzým ornitíntranskarbamyláza zavedená do lipidových nanočastíc | Liečba nedostatku transkarbamylázy ornitínu |
| Slovenian | Spremenjen messenger ribonukleinske kisline, ki kodira encim humane ornitinske transkarbamoilaze inkapsuliran v lipidnih nanodelcih | Zdravljenje pomanjkanja ornitin-transkarbamilaze |
| Spanish | Ácido ribonucleico mensajero modificado que codifica la enzima ornitina transcarbamilasa humana encapsulada en nanopartículas lipídicas | Tratamiento de la deficiencia de ornitina transcarbamilasa |
| Swedish | Modifierad budbärarribonukleinsyra som kodar för humant ornitintranskarbamylas enzym inkapslat i lipida nanopartiklar | Behandling av brist på ornitintranskarbamylas |

| Language | Active ingredient | Indication |
|---|---|---|
| Norwegian | Modifisert messenger ribonukleinsyre som koder for humant ornitintranskarbamylaseenzym innkapslet i lipide nanopartikler | Behandling av ornitintranskarbamylase-mangel |
| Icelandic | Aðlöguð mótandi ríbósakjarnsýra sem kóðar fyrir omitin transkarbamýlasaensími sem er komið fyrir  í blóðfitu nanóögnum | Meðferð við skorti á ornitín transkarbamýlasa |