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Public summary of opinion on orphan designation

Codon-optimised human ornithine transcarbamylase mRNA complexed with lipid-based nanoparticles for the treatment of ornithine transcarbamylase deficiency

On 27 June 2018, orphan designation (EU/3/18/2033) was granted by the European Commission to Real Regulatory Limited, Ireland, for codon-optimised human ornithine transcarbamylase mRNA complexed with lipid-based nanoparticles (also known as MRT5201) 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 517,400,000 (Eurostat 2018).

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

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. Laboratory studies show that it restores the levels of ornithine transcarbamylase in the liver, which is missing in patients affected by the condition. 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 tiny fatty particles to protect it and help it enter liver cells. When given by infusion (drip) into a vein, the medicine is expected to enable liver cells to produce ornithine transcarbamylase and to 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 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 24 May 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	Activeingredient	Indication
English	Codon-optimised human ornithine transcarbamylase mRNA complexed with lipid-based nanoparticles	Treatment of ornithine transcarbamylase deficiency
Bulgarian	Кодон-оптимизирана иРНК, кодираща човешка орнитин транскарбамилаза, свързана с наночастици, базирани на липиди	Лечение на дефицит на орнитин транскарбамилаза
Croatian	mRNA s optimiziranim kodonima za ljudsku ornitin-transkarbamilazu u kompleksu s nanočesticama na bazi lipida	Liječenje nedostatka ornitin-transkarbamilaze
Czech	Humánní mRNA pro ornithin transkarbamylázu s optimalizovaným kodonem v komplexu s nanočásticemi na bázi lipidů	Léčba nedostatku transkarbamylázy ornithine
Danish	Kodonoptimeret human ornithintranscarbamylase-mRNA kompleksbundet med lipidbaserede nanopartikler	Behandling af ornithin transcarbamylase defect
Dutch	Codongeoptimaliseerd humaan ornithinetranscarbamylase mRNA gecomplexeerd met nanopartikels op basis van lipiden	Behandeling van ornithine transcarbamylase deficiëntie
Estonian	Lipiidipõhiste nanoosakestega kompleksi moodustanud koodonoptimeeritud inimese ornitiintranskarbamülaasi mRNA	Ornitiintranskarbamülaasi puudulikkuse ravi
Finnish	Kodonioptimoitu, lipidinanopartikkeleilla kompleksoitu ihmisperäinen ornitiinitranskarbamylaasin mRNA	Ornitiinitranskarbamylaasin puutoksen hoito
French	Complexe d'ARNm codant pour l'ornithine carbamyl transférase humaine et de nanoparticules lipidiques avec optimisation des codons	Traitement du déficit en ornithine transcarbamylase
German	Codon-optimierte humane Ornithin-Transcarbamylase-mRNA komplexiert mit lipidbasierten Nanopartikeln	Behandlung des Ornithintranscarbamylase-Mangels
Greek	Βελτιστοποιημένων κωδικονίων mRNA τρανσκαρβαμυλάσης της ορνιθίνης συμπλοκοποιημένο με λιπιδικά νανοσωματίδια	Θεραπεία της έλλειψης της τρανσκαρβαμυλάσης της ορνιθίνης
Hungarian	Lipid alapú nanorészecskékkel komplexált kodonoptimalizált humán ornitin-transzkarbamiláz mRNS	Ornitin transzkarbamiláz hiány kezelése
Italian	mRNA con codoni ottimizzati, codificante l'ornitina transcarbamilasi umana, complessato con nanoparticelle a base lipidica	Trattamento del deficit di ornitina-transcarbamilasi
Latvian	Cilvēka ornitīna transkarbamilāzes mRNS ar optimizētu kodonu, kas kompleksēta ar lipīdu bāzes nanodaļiņām	Ornitīna transkarbamilāzes nepietiekamības ārstēšana
Lithuanian	Kodonas, optimizuotas žmogaus ornitino transkarbomilazės iRNR, komplekse su lipido pagrindo nanodalelėmis	Ornitintranskarbamilazės stokos gydymas

[1] At the time of designation

Language	Activeingredient	Indication
Maltese	Ornitin transkarbamilaži uman ottimizzat b'kodon b'kumpless ta' mRNA b'nanopartiċelli bbażati fuq il-lipidi	Kura ta' defiċjenza ta' l-Ornithine Transcarbamylase
Polish	mRNA z zoptymalizowanym kodonem kodujący ludzką transkarbamylazę ornitynową skompleksowany z nanocząstkami na bazie lipidów	Leczenie pacjentów z niedoborem transkarbamylazy ornitynowej
Portuguese	Complexo de mRNA da ornitina transcarbamilase humana otimizado por codão com nanopartículas à base de lípidos	Tratamento da deficiência de ornitina-transcarbamilase
Romanian	ARNm al ornitin-transcarbamilazei umane cu optimizare a codonului în complex cu nanoparticule lipidice	Tratamentul deficitului de ornitin- transcarbamilază
Slovak	Ľudská mRNA pre ornitíntranskarbamylázu s optimalizovaným kodónom v komplexe s nanočasticami na báze lipidov	Liečba nedostatku transkarbamylázy ornitínu
Slovenian	mRNA z optimiziranim kodonom za človeško ornitintranskarbamilazo, združena z nanodelci na osnovi lipidov	Zdravljenje pomanjkanja ornitin-transkarbamilaze
Spanish	Complejo formado por ARNm con codones optimizados para ornitina transcarbamilasa humana y nanopartículas lipídicas	Tratamiento de la deficiencia de ornitina transcarbamilasa
Swedish	Kodonoptimerat humant ornitintranskarbamylas-mRNA sammansatt med lipidbaserade nanopartiklar	Behandling av brist på ornitintranskarbamylas
Norwegian	Kodonoptimalisert human ornitintranskarbamylase mRNA i kompleks med lipidbaserte nanopartikler	Behandling av ornitintranskarbamylase-mangel
Icelandic	Táknahámarkað ornitíntranskarbamýlasa mRNA manna sem flétta með nanóögnum í lípíðgrunni	Meðferð við skorti á ornitín transkarbamýlasa