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Public summary of opinion on orphan designation

Synthetic double-stranded siRNA oligonucleotide directed against lactate dehydrogenase A mRNA and containing four modified nucleosides which form a ligand cluster of four N-acetylgalactosamine residues for the treatment of primary hyperoxaluria

On 31 July 2018, orphan designation (EU/3/18/2052) was granted by the European Commission to Dicerna EU Limited, United Kingdom, for synthetic double-stranded siRNA oligonucleotide directed against lactate dehydrogenase A mRNA and containing four modified nucleosides which form a ligand cluster of four N-acetylgalactosamine residues (also known as DCR-L1360) for the treatment of primary hyperoxaluria.

What is primary hyperoxaluria?

Primary hyperoxaluria is an inherited disease in which patients suffer from recurring kidney and bladder stones which lead to pain, blood in the urine and frequent urinary tract infections. The disease is caused by the lack of certain enzymes produced by the liver that are needed to breakdown a substance called glyoxylate in the body. Instead of being converted into the amino acid glycine, glyoxalate is therefore converted into excess oxalate. This can form calcium oxalate deposits, which cause kidney and bladder stones and may damage the kidneys and other organs.

Primary hyperoxaluria is long-term debilitating and life threatening because of the high rate of kidney failure seen in patients with the condition.

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

At the time of designation, primary hyperoxaluria 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).

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What treatments are available?

At the time of designation, no satisfactory methods were authorised in the EU for treating primary hyperoxaluria. Different treatments were used to prevent the accumulation of calcium oxalate such as dietary changes, drinking plenty of fluids and taking vitamin B6. Kidney and liver transplantation have been possible options in patients with kidney failure.

How is this medicine expected to work?

The conversion of glyoxylate to oxalate in patients with primary hyperoxaluria is controlled by an enzyme called lactate dehydrogenase. This medicine is made of a small strand of synthetic genetic material, called 'small interfering RNA' (siRNA), that is expected to enter liver cells and stop them from making lactate dehydrogenase. This in turn reduces the production of oxalate and so decreases the risk of calcium oxalate deposits from forming and damaging the kidneys and other organs.

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 primary hyperoxaluria had been started.

At the time of submission, the medicine was not authorised anywhere in the EU for primary hyperoxaluria 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 21 June 2018 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	Synthetic double-stranded siRNA oligonucleotide directed against lactate dehydrogenase A mRNA and containing four modified nucleosides which form a ligand cluster of four N-acetylgalactosamine residues	Treatment of primary hyperoxaluria
Bulgarian	Синтетичен двойно-верижен siРНК олигонуклеотид, насочен срещу иРНК за лактат дехидрогеназа А, съдържащ 4 модифицирани нуклеозиди, формиращи лиганден кластер от 4 N-ацетилгалактозаминови остатъка	Лечение на първична хипероксалурия
Croatian	Sintetski dvolančani siRNA oligonukleotid usmjeren na mRNA laktat dehidrogenaze A koji sadrži četiri modificirana nukleozida koji tvore ligandni skup od četiri N-acetilgalaktozaminska ostatka	Liječenje primarne hiperoksalurije
Czech	Syntetický dvou vláknový siRNA oligonukleotid směrovaný proti mRNA laktát dehydrogenázy a obsahující čtyři modifikované nukleosidy, které tvoří clustr ligandů 4 N-acetylgalaktosaminových residuí	Léčba primární hyperoxalurie
Danish	Syntetisk dobbelt-strenget SiRNA oligonucleotid indeholdende fire modificerede nucleosider formende et N-acetylgalactosamine residuens rettet mod laktat dehydrogenase A mRNA	Behandling af primær hyperoxaluri
Dutch	Synthetisch dubbel-strengig siRNA oligonucleotide gericht tegen lactaat dehydrogenase A mRNA en welke vier gemodificiëerde nucleosiden bevat die een ligand cluster van vier N-acetylgalactosamine residueën vormt	Behandeling van primaire hyperoxalurie
Estonian	Laktaadi dehüdrogenaas A mRNA vastu suunatud sünteetiline kaheahelaline siRNA oligonukleotiid, mis sisaldab nelja N-atsetüülgalaktoosamiini jäägiga ligandiklastrit moodustavat nelja modifitseeritud nuleosiidi	Esmase hüperoksaluuria ravi
Finnish	Synteettinen, kaksoiskierteinen siRNA oligonukleotidi, jonka kohteena on laktaattidehydrogenaasi A:n mRNA ja joka sisältää neljä muokattua nukleosidiä, jotka muodostavat neljä N-asetyyligalaktosamiini-jäämää sisältävän ligandi klusterin	Primaarisen hyperoksalurian hoito
French	Oligonucleotide d'ARNsi synthetique double-helice contre l'ARNm de la lactate déshydrogénase A contenant 4 nucleoside modifies formant un sous-ensemble de 4 residus N-acetylgalactosamine	Traitement de l'hyperoxalurie primaire

[1] At the time of designation

Language	Active ingredient	Indication
German	Synthetisches doppelsträngiges siRNA Oligonukleotid das gegen die mRNA der Laktat Dehydrogenase A gerichtet ist und 4 modifizierte Nukeloside enthält, die einen Liganden-Cluster aus 4 N-Acetylgalactosaminen formen	Behandlung der primären Hyperoxalurie
Greek	Συνθετικό δίκλωνο siRNA ολιγονουκλεοτίδιο έναντι του mRNA της γαλακτικής αφυδρογονάσης Α, που περιέχει ένα πρόσδεμα συμπλέγματος με τέσσερα υπολείμματα Ν-ακετυλογαλακτοσαμίνης	Θεραπεία της πρωτοπαθούς υπεροξαλουρίας
Hungarian	Laktát-dehidrogenáz A mRNS elleni célzott szintetikus kettős szálú siRNS oligonukleotid ami négy módosított nukeozidot tartalmaz melyek négy N-acetilgalaktózamin maradvány ligand klaszterét formázzák	Primer hiperoxaluria kezelésére
Italian	Oligonucleotide sintetico siRNA a doppia catena diretto contro il mRNA della lattato-deidrogenasi A, contenente quattro nucleosidi modificati che formano un gruppo di ligandi di quattro residui di N-acetilgalattosamina.	Trattamento delll'iperossaluria primaria
Latvian	Sintētisks dubultķēdes siRNS oligonukleotīds, kas vērsts pret laktātdehidrogenāzes A mRNS un satur četrus modificētus oligonukleozīdus, kas veido četru N-acetilgalaktozamīna atlikumu ligandu kopu	Primāras hiperoksalūrijas ārstēšana
Lithuanian	Sintetinis dvigrandis siRNR oligonukleotidas, nukreiptas prieš laktato dehidrogenazės A iRNR ir turintis keturis modifikuotus nukleozidus, kurie formuoja ligando klasterį iš keturių N-acetilgalaktozamino liekanų	Pirminės hiperoksalurijos gydymas
Maltese	Oligonukleotid sintetiku tal-siRNA b'katina doppja dirett kontra mRNA ta' lattatdeidroġenaży A u li fih erba' nukleosidi modifikati li jiffurmaw ġabra ta' ligand ta' erba' residwi N-aċetilgalattosamina	Kura ta' iperoxalurja primarja
Polish	Syntetyczny dwuniciowy oligonukleotyd siRNA skierowany przeciwko mRNA dehydrogenazy A mleczanu i zawierajcy cztery modyfikowane nukleozydy które tworza zgrupowany ligand czterech resztek N-acetylgalaktozoaminy	Leczenie pierwotnej hiperoksalurii
Portuguese	Oligonucleotídeo sintético de siRNA de cadeia dupla direcionado contra o ARNm da lactato desidrogenase A e contendo quatro nucleosídeos modificados que formam um ligante composto por quatro resíduos de N-acetilgalactosamina aglomerados	Tratamento da hiperoxalúria primária
Romanian	Oligonucleotid sintetic siARN dublu catenar ce ţinteşte ARNm-ul lactat-dehidrogenazei A şi care conţine patru nucleozide modificate ce formează un grup de liganzi format din patru reziduuri de N-acetilgalactozamină	Tratamentul hiperoxaluriei primare

Language	Active ingredient	Indication
Slovak	Syntetický dvoj-vláknový siRNA oligonukleotid namierený proti mRNA laktátovej dehydrogenázy A, obsahujúci štyri modifikované nukleozidy, ktoré vytvárajú ligandové zoskupenia v počte štyroch N-acetylgalaktozamínových zvyškov	Liečba primárnej hyperoxalúrie
Slovenian	Synthetični oligonukleotid dvojno verižne siRNA usmerjen proti mRNA laktatne dehidrogenaze A, in ki vsebuje štiri modificirane nukleozide, ki tvorijo ligand gruče štirih rezidualnih N-acetilgalaktozaminov	Zdravljenje primarne hiperoksalurije
Spanish	ARNsi sintético de cadena doble dirigido contra la ARNm de la dehydrogenase lactica y que contiene cuatro nucleosides modificados que estan agrupados y liados a cuatro residuos de N-acetilgalactosamina	Tratamiento de la hiperoxaluria primaria
Swedish	Syntetiskt dubbelsträngat siRNA-oligonukleotid mot laktatdehydrogenas A mRNA, innehållande fyra modifierade nukleosider som bildar ett ligandkluster av fyra N-acetylgalactosaminrester	Behandling av primär hyperoxaluri
Norwegian	Syntetisk dobbeltrådet siRNA oligonukleotid rettet mot laktat dehydrogenase A mRNA og inneholder fire modifiserte nukleosider som danner et ligandkluster av fire N-acetylgalaktosamin-enheter	Behandling av primær hyperoksaluri
Icelandic	Samtengt tvíþátta siRNA fákirni beint gegn mRNA fyrir laktat dehýdrógenasa með fjórum breyttum núkleósíðum sem mynda klasabindil fjögurra leifa N-acetýlgalaktósamíns	Meðferð við prímeri oxalatmigu