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Committee for Orphan Medicinal Products

Public summary of opinion on orphan designation

Synthetic double-stranded siRNA oligonucleotide directed against hydroxyacid oxidase 1 mRNA and covalently linked to a ligand containing three N-acetylgalactosamine residues for the treatment of primary hyperoxaluria

On 21 March 2016, orphan designation (EU/3/16/1637) was granted by the European Commission to Alnylam UK Limited, United Kingdom, for synthetic double-stranded siRNA oligonucleotide directed against hydroxyacid oxidase 1 mRNA and covalently linked to a ligand containing three N-acetylgalactosamine residues for the treatment of primary hyperoxaluria.

What is primary hyperoxaluria?

Primary hyperoxaluria is an inherited disease caused by the lack of certain enzymes needed to breakdown a substance called glyoxylate in the body. Patients with primary hyperoxaluria have high levels of oxalate in the urine, because glyoxylate instead of being converted into the amino acid glycine is converted into excess oxalate. Oxalate can form calcium oxalate deposits, which can cause stones in the kidney and urinary tract (structures that carry urine) as well as injury to other organs such as the heart, eyes, bones and skin. Characteristic symptoms of the disease include blood in the urine, tummy pain and frequent urinary tract infections.

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 0.05 in 10,000 people in the European Union (EU). This was equivalent to a total of around 2,600 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 513,700,000 (Eurostat 2016).

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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 certain cases.

How is this medicine expected to work?

This medicine is expected to reduce the body's production of glyoxylate, the substance that is converted to oxalate in patients with primary hyperoxaluria. Normally, production of glyoxylate is regulated by an enzyme called hydroxyacid oxidase (also known as glycolate oxidase). The medicine is designed to attach specifically to genetic material in the cell responsible for the production of hydroxyacid oxidase. This blocks production of the enzyme so that less glyoxylate is created, thereby reducing the production of oxalate. Therefore, the chance of forming calcium oxalate deposits is reduced.

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 18 February 2016 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 hydroxyacid oxidase 1 mRNA and covalently linked to a ligand containing three N-acetylgalactosamine residues	Treatment of primary hyperoxaluria
Bulgarian	Синтетичен двойноверижен siРНК олигонуклеид насочен срещу иРНК на хидроксикисела оксидаза 1, ковалентно свързан с лиганд, съдържащ три остатъка от N-ацетилгалактозамин	Лечение на първична хипероксалурия
Croatian	Sintetski dvostruki lanac siRNA oligonukleotida usmjeren protiv hidroksikiselinske oksidaze 1 mRNA koja je kovalentno vezana na ligand koji sadrži tri ostataka N-acetilgalaktozamina	Liječenje primarne hiperoksalurije
Czech	Syntetický dvouvláknový oligonukleotid siRNA nasměrovaný proti hydroxykyselině oxidázy 1 mRNA, který je kovalentně spojený s ligandem obsahujícím tři rezidua N-acetylgalaktosaminu	Léčba primární hyperoxalurie
Danish	Syntetisk dobbeltstrenget siRNA oligonukleotid rettet mod hydroxysyre oxidase 1 mRNA, som er kovalent bundet til en ligand indeholdende tre N-acetylgalactosamin rester	Behandling af primær hyperoxaluri
Dutch	Synthetisch dubbelstrengig siRNA oligonucleotide gericht tegen hydroxyzuur oxidase 1 mRNA dat covalent gebonden is aan een ligand die drie N-acetylgalactosamine resten bevat	Behandeling van primaire hyperoxalurie
Estonian	Sünteetiline kaheahelaline siRNA oligonukleotiid, mis on suunatud hüdroksühappe oksüdaasi 1 mRNA vastu ja mis on kovalentselt seotud kolme N-atsetüülgalaktosamiini jääki sisaldava ligandiga	Esmase hüperoksaluuria ravi
Finnish	Synteettinen, hydroksidi-oksidaasi 1 mRNA:ta vastaan suunnattu kaksijuosteinen siRNA-oligonukleotidi. Tämä oligonukleotid on kovalenttisesti yhdistetty ligandiin, joka sisältää kolme N-asetyyligalaktosamiini tähdettä.	Primaarisen hyperoksalurian hoito
French	Oligonucléotide siRNA double brin synthétique dirigé contre l'ARNm de l'hydroxyacide oxydase 1 lié de manière covalente à un ligand contenant trois résidus N-acétylgalactosamine	Traitement de l'hyperoxalurie primaire
German	Synthetisches doppelsträngiges siRNA-Oligonukleotid gegen Hydroxysäure-Oxidase 1 mRNA, kovalent verknüft mit einem Liganden, der drei *N*-Acetylgalactosamin Reste enthält	Behandlung der primären Hyperoxalurie

[1] At the time of designation

Language	Active ingredient	Indication
Greek	Συνθετικό διπλής έλικας ολιγονουκλεοτίδιο siRNA κατευθυνόμενο εναντίον του mRNA της οξειδάσης υδροξυοξέος -1 το οποίο συνδέεται ομοιοπολικά με συνδέτη περιέχοντα τρία υπολείμματα N-ακετυλογαλακτοσαμίνης	Θεραπεία της πρωτοπαθούς υπεροξαλουρίας
Hungarian	A három N-acetil-galaktózamin maradékot tartalmazó ligandhoz kovalens kötéssel kapcsolódó hydroxyacid oxidáz 1 mRNA ellen irányuló szintetikus kettős szálú siRNA oligonukleotid	Primer hiperoxaluria kezelésére
Italian	Oligonucleotide sintetico con siRNA a doppio filamento diretto contro mRNA idrossiacido ossidasi 1, legato in modo covalente ad un legante contenente tre residui di N-acetilgalattosamina	Trattamento delll'iperossaluria primaria
Latvian	Sintētisks dubultspirāles siRNS oligonukleotīds, kas vērsts pret hidroksiskābes oksidāzes 1 mRNS un ir kovalenti saistīts ar trīs N-acetilgalaktozamīna atliekas saturošu ligandu	Primāras hiperoksalūrijas ārstēšana
Lithuanian	Sintetinis dvigrandis siRNR oligonukleotidas, nukreiptas prieš hidroksirūgšties oksidazės 1 mRNR, ir kovalentiškai susietas su ligandu, turinčiu tris N-acetilgalaktozamino liekanas	Pirminės hiperoksalurijos gydymas
Maltese	Oligonukleotid sintetiku tas-siRNA b'katina doppja dirett kontra *hydroxyacid oxidase 1 mRNA* u magħqud b'mod kovalenti ma' ligand li fih tliet residwi ta' N-acetylgalactosamine	Kura ta' iperoxalurja primarja
Polish	Syntetyczny dwuniciowy oligonukleotyd siRNA skierowany przeciwko mRNA oksydazy hydroksykwasów 1 połączony kowalentnie z ligandem zawierającym trzy reszty N-acetylgalaktozaminy	Leczenie pierwotnej hiperoksalurii
Portuguese	Oligonucleótido sintético de ARNsi de cadeia dupla dirigido contra a ARNm de hidroxiácido oxidase 1 ligada de forma covalente a um ligando contendo três resíduos de N-acetilgalactosamina	Tratamento da hiperoxalúria primária
Romanian	Oligonucleotidă siARN cu catenă dublu-spiralată, sintetică, orientată împotriva oxidazei hidroxiacide 1 mARN legată covalent la un ligand care conţine trei reziduuri de N-acetilgalactozamină	Tratamentul hiperoxaluriei primare
Slovak	Syntetický dvojvláknový oligonukleotid siRNA nasmerovaný proti hydroxykyseline oxidázy 1 mRNA, ktorý je kovalentne spojený s ligandom obsahujúcim tri rezíduá N-acetylgalaktosamínu	Liečba primárnej hyperoxalúrie typu 1
Slovenian	Sintetični oligonukleotid male dvoverižne interferenčne RNA, usmerjen proti hidroksikislinski oksidazi 1 informacijske RNA in je kovalentno povezan na ligand, ki vsebuje tri ostanke N-acetilgalaktozamina	Zdravljenje primarne hiperoksalurije

Language	Active ingredient	Indication
Spanish	Oligonucleótido sintético con ARNip bicatenario dirigido contra el ARNm de la hidroxiácido oxidasa 1 unido covalentemente a un ligando que contiene tres residuos de N-acetilgalactosamina	Tratamiento de la hiperoxaluria primaria
Swedish	Synthetisk dubbelsträngad siRNA-oligonukleotid riktad mot hydroxisyra-oxidas 1 mRNA som är kovalent bunden till en ligand innehållande tre residuum av acetylgalaktosaktosamin	Behandling av primär hyperoxaluri
Norwegian	Syntetisk dobbeltstrenget siRNA oligonukleotid rettet mot hydroksysyre-oksydase 1 mRNA som er kovalent knyttet til et ligand som inneholder tre rester av N-acetylgalaktosamin	Behandling av primær hyperoksaluri
Icelandic	Tilbúini tvístrengja sIRNA ólígónúkleótíð beint gegn hýdroxýsýru oxidasa 1 mRNA sem er samgilt tengt við tengil sem inniheldur þrjár N-acetýlgaalaktósamí n leifar	Meðferð við fyrsta stigs sólarhringsútskilnaði