22 September 2016
EMA/COMP/510078/2016
Committee for Orphan Medicinal Products

Public summary of opinion on orphan designation

Synthetic double-stranded siRNA oligonucleotide directed against delta-aminolevulinic acid synthase 1 mRNA, covalently linked to a ligand containing three N-acetylgalactosamine residues for the treatment of acute hepatic porphyria

On 29 August 2016, orphan designation (EU/3/16/1731) was granted by the European Commission to Alnylam UK Limited, United Kingdom, for synthetic double-stranded siRNA oligonucleotide directed against delta-aminolevulinic acid synthase 1 mRNA, covalently linked to a ligand containing three N-acetylgalactosamine residues (also known as ALN-AS1) for the treatment of acute hepatic porphyria.

What is acute hepatic porphyria?

Acute hepatic porphyria is a genetic condition in which patients lack certain enzymes needed to produce haem, a component of the blood pigment haemoglobin. As a result, substances for making haem accumulate in the body (particularly in the liver) and become toxic, causing attacks of severe abdominal pain, vomiting and nervous system disorders, such as seizures (fits), depression and anxiety. Some patients may also experience skin problems, with skin becoming oversensitive to light.

Acute hepatic porphyria is life-threatening due to the possibility of paralysis and respiratory arrest during attacks and debilitating in the long term because of symptoms such as pain, nausea, seizures and skin blistering.

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

At the time of designation, acute hepatic porphyria 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 513,700,000 (Eurostat 2016).

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What treatments are available?

At the time of the orphan designation, Normosang (haem arginate) was authorised for treating acute hepatic porphyria in the EU. Patients also received supportive treatment to relieve the symptoms of the disease, including pain killers and antiemetics (to treat nausea and vomiting). In some patients, liver transplantation was performed.

The sponsor has provided sufficient information to show that this medicine might be of significant benefit for patients with the condition, with laboratory studies showing that it may be faster at reducing the levels of the toxic substances than the authorised product. In addition, a single injection of this medicine is expected to have a long-lasting effect. These assumptions 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?

This medicine is made of a short, synthetic strand of genetic material called 'small interfering RNA' (siRNA) that has been designed to interfere with the production of an enzyme involved in an early step in making haem. By blocking this early step of haem production in patients with acute hepatic porphyria, the medicine is expected to prevent the next steps which produce substances that accumulate in the body and cause the symptoms of the disease.

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, clinical trials with the medicine in patients with acute hepatic porphyria had not yet started.

At the time of submission, the medicine was not authorised anywhere in the EU for acute hepatic porphyria 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 13 July 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 delta-aminolevulinic acid synthase 1 mRNA covalently linked to a ligand containing three N-acetylgalactosamine residues	Treatment of acute hepatic porphyria
Bulgarian	Синтетичен двойноверижен олигонуклеид от къса интерферентна РНК (siRNA), насочен срещу иРНК на делта-аминолевулинова киселина синтаза 1, ковалентно свързана с лиганд, съдържащ три N-ацетилгалактозаминови остатъци	Лечение на остра чернодробна порфирия
Croatian	Sintetski oligonukleotid dvolančane siRNA usmjeren protiv delta-aminolevulinske kiselinske sintaze 1 mRNA koja je kovalentno vezana na ligand koji sadrži tri ostatka N-acetilgalaktozamina	Liječenje akutne hepatičke porfirije
Czech	Syntetický dvouvláknový oligonukleotid siRNA nasměrovaný proti mRNA pro syntázu 1 delta-aminolevulové kyseliny, který je kovalentně spojený s ligandem obsahujícím tři rezidua N-acetylgalaktosaminu	Léčba akutní hepatální porfyrie
Danish	Syntetisk dobbeltstrenget siRNA-oligonukelotid rettet mod delta-aminolevulinsyresyntase 1-mRNA, som er kovalent bundet til en ligand indeholdende tre N-acetylgalactosamin-enheder	Behandling af akut hepatisk porfyri
Dutch	Synthetisch dubbelstrengig siRNA oligonucleotide gericht tegen delta-aminolevulinezuur synthase 1 mRNA dat covalent gebonden is aan een ligand die drie N-acetylgalactosamineresten bevat	Behandeling van acute hepatische porfyrie
Estonian	Sünteetiline kaheahelaline siRNA oligonukleotiid, mis on suunatud deltaaminolevuliinhappe süntaasi 1 mRNA vastu ja on kovalentselt seotud kolme N-atsetüülgalaktosamiini jääki sisaldava ligandiga	Ägeda maksaporfüüria ravi
Finnish	Delta-aminolevuliinihapposyntaasi 1 -mRNA:ta vastaan suunnattu synteettinen kaksijuosteinen siRNA-oligonukleotidi, joka on kovalenttisesti sitoutunut kolmea N-asetyyligalaktosamiinijäämää sisältävään ligandiin	Akuutin maksaporfyrian hoito
French	Oligonucléotide siRNA double brin synthétique dirigé contre l'ARNm de l'acide delta-aminolévulinique synthase 1 lié de façon covalente à un ligand contenant trois résidus N-acétylgalactosamine	Traitement de la porphyrie hépatique aiguë

[1] At the time of designation

Language	Active ingredient	Indication
German	Synthetisches doppelsträngiges siRNA-Oligonukleotid gegen δ-Aminolävulinsäuresynthase-1-mRNA, kovalent verknüpft mit einem drei *N*-Acetylgalactosamin-Reste enthaltenden Liganden	Behandlung der akuten hepatischen Porphyrie
Greek	Συνθετικό διπλής έλικας ολιγονουκλεοτίδιο siRNA κατευθυνόμενο εναντίον mRNA 1 συνθετάσης του δ-αμινολεβουλινικού οξέος, το οποίο συνδέεται ομοιοπολικά με συνδέτη περιέχοντα τρία υπολείμματα N-ακετυλογαλακτοσαμίνης	Θεραπεία της Οξείας Ηπατικής Πορφυρίας
Hungarian	A három N-acetil-galaktózamin maradékot tartalmazó ligandhoz kovalens kötéssel kapcsolódó delta-aminolevulinsav-szintáz-1 mRNS ellen irányuló szintetikus kettős szálú siRNS oligonukleotid	Akut hepatikus porphyria kezelése
Italian	Oligonucleotide sintetico con siRNA a doppio filamento diretto contro mRNA acido delta-aminolevulinico sintasi 1, legato in modo covalente ad un legante contenente tre residui di N-acetilgalattosamina	Trattamento della porfiria epatica acuta
Latvian	Sintētisks divpavedienu siRNS oligonukleotīds, kas vērsts pret delta-aminolevulīnskābes sintāzes 1 mRNS un ir kovalenti saistīts ar trīs N-acetilgalaktozamīna atlikumus saturošu ligandu	Akūtas aknu porfīrijas ārstēšanai
Lithuanian	Sintetinis dvigrandis siRNR oligonukleotidas, nukreiptas prieš delta-aminolevulino rūgšties sintazę 1 mRNR, kovalentiškai susietą su ligandu, turinčiu tris N-acetilgalaktozamino liekanas	Ūminės kepenų porfirijos gydymas
Maltese	Oligonukleotide sintetiku tas-siRNA b'katina doppja dirett kontra delta-aminolevulinic acid synthase 1 mRNA magħqud b'mod kovalenti ma' ligand li fih tliet residwi N-acetylgalactosamine	Kura tal-porfirja epatika akuta
Polish	Syntetyczny dwuniciowy oligonukleotyd siRNA skierowany przeciwko mRNA syntazy kwasu delta-aminolewulinowego 1 połączony kowalencyjnie z ligandem zawierającym trzy reszty N-acetylogalaktozaminy	Leczenie ostrej porfirii wątrobowej
Portuguese	Oligonucleótido ARNsi de cadeia dupla sintético dirigido contra o ARNm do ácido delta-aminolevulínico sintase 1 ligada de forma covalente a um ligante contendo três resíduos de N-acetilgalactosamina	Tratamento da porfiria hepática aguda
Romanian	Oligonucleotidă siARN cu catenă dublă, sintetică, orientată împotriva ARNm al sintazei 1 a acidului delta-aminolevulinic legată covalent la un ligand care conţine trei reziduuri de N-acetilgalactozamină	Tratamentul porfiriei hepatice acute

Language	Active ingredient	Indication
Slovak	Syntetický dvojvláknový oligonukleotid siRNA nasmerovaný proti mRNA pre syntázu 1 kyseliny delta-aminolevulovej, ktorý je kovalentne viazaný s ligandom obsahujúcim tri rezíduá N-acetylgalaktózamínu	Liečba akútnej hepatálnej porfýrie
Slovenian	Sintetični dvoverižni oligonukleotid siRNA, usmerjen proti mRNA sintetaze 1 delta-aminolevulinske kisline, ki je kovalentno vezana na ligand, ki vsebuje tri N-acetilgalaktozaminske ostanke	Zdravljenje akutne hepatične porfirije
Spanish	Oligonucleótido sintético con ARNip bicatenario dirigido contra el ARNm de la δ-aminolevulinato sintasa 1, unido covalentemente a un ligando que contiene tres residuos de N-acetilgalactosamina	Tratamiento de la porfiria hepática aguda
Swedish	Syntetisk dubbelsträngad siRNA-oligonukleotid riktad mot deltaaminolevulinsyra-syntas 1 mRNA, som är kovalent bunden till en ligand innehållande tre återstoder av N-acetylgalaktosamin	Behandling av akut hepatisk porfyri
Norwegian	Syntetisk dobbelttrådet siRNA-oligonukleotid rettet mot delta-aminolevulinsyre syntase 1 mRNA som er kovalent knyttet til et ligand som inneholder tre rester av N-acetylgalaktosamin enheter	Behandling av akutt hepatisk porfyri
Icelandic	Tilbúið tveggja þátta siRNA fákirni sem beinist gegn delta-amínólevúlín-sýrusýntasa 1 mRNA sem er tengt samgilt við bindil sem inniheldur þrjár N-asetýlgalaktósaamínleifar	Meðferð við bráðri lifrarporfýríu