27 August 2014
EMA/COMP/360847/2014
Committee for Orphan Medicinal Products

Public summary of opinion on orphan designation

Synthetic double-stranded siRNA oligonucleotide directed against antithrombin mRNA and covalently linked to a ligand containing three N-acetylgalactosamine residues for the treatment of haemophilia A

On 29 July 2014, orphan designation (EU/3/14/1297) was granted by the European Commission to Alnylam UK Limited, United Kingdom, for synthetic double-stranded siRNA oligonucleotide directed against antithrombin mRNA and covalently linked to a ligand containing three N-acetylgalactosamine residues for the treatment of haemophilia A.

What is haemophilia A?

Haemophilia A is an inherited bleeding disorder that is caused by the lack of factor VIII, which is one of the proteins involved in the blood coagulation (clotting) process. Patients with haemophilia A are more prone to bleeding than normal and have prolonged bleeding after injury or surgery. Bleeding can also happen within muscles or the spaces in the joints, such as the elbows, knees and ankles. This can lead to permanent injury if it happens repeatedly.

Haemophilia A is a debilitating disease that is life-long and may be life threatening because bleeding can happen in the brain, the spinal cord or the gut.

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

At the time of designation, haemophilia A affected less than 1 in 10,000 people in the European Union (EU). This was equivalent to a total of fewer than 51,000 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).

What treatments are available?

At the time of designation, medicines containing factor VIII were authorised in the EU for the treatment of haemophilia A, to replace the missing protein. However, not all patients with

*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 511,100,000 (Eurostat 2014).

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haemophilia A could benefit from these medicines because the immune system (the body's natural defences) can react against them by producing 'inhibitors' (antibodies) against factor VIII. In these cases, other treatments were used, such as medicines containing other coagulation factors such as factor VIIa, either alone or as part of combination treatment.

The sponsor has provided sufficient information to show that this medicine might be of significant benefit for patients with haemophilia A because early studies in experimental models indicate that it could be used to control bleeding in haemophilia A patients who have developed inhibitors against factor VIII. 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?

This medicine is made of a small strand of synthetic genetic material, called 'small interfering RNA' (siRNA), that has been designed to interfere with or block the gene for the protein antithrombin, thereby reducing its production. In the body, antithrombin blocks thrombin, one of the substances involved in blood clotting. By reducing the production of antithrombin, the medicine is expected to increase the clotting capacity of the blood in patients with haemophilia A.

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 haemophilia A were ongoing.

At the time of submission, the medicine was not authorised anywhere in the EU for haemophilia A. Orphan designation of the medicine had been granted in United States for this condition.

In accordance with Regulation (EC) No 141/2000 of 16 December 1999, the COMP adopted a positive opinion on 12 June 2014 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:

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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 antithrombin mRNA and covalently linked to a ligand containing three N-acetylgalactosamine residues	Treatment of haemophilia A
Bulgarian	Синтетичен, двойно-спирален siRNA олигонуклеотид, насочен срещу антитромбинова mRNA, ковалентно свързан с лиганд, съдържащ три остатъка на N-ацетил галактозамин	Лечение на хемофилия А
Croatian	Sintetički oligonukleotid siRNK s dvostrukim lancem usmjeren protiv mRNK za antitrombin, kovaletno vezan za ligand koji sadrži tri N-acetilgalaktozaminske skupine	Liječenje hemofilije A
Czech	Oligonukleotid syntetické dvouvláknové siRNA namířený proti mRNA antitrombinu, který je kovalentně spojen s ligandem obsahujícím tři rezidua N-acetylgalaktosaminu	Léčba hemofilie A
Danish	Syntetisk dobbeltstrenget siRNA oligonukleotid rettet mod antihrombin mRNA, og kovalent bundet til en ligand indeholdende tre N-acetylgalactosamin rester	Behandling af hæmofili A
Dutch	Synthetisch dubbelstrengig siRNA oligonucleotide gericht tegen antitrombine mRNA dat covalent gebonden is aan een ligand dat drie N-acetylgalactosamine residuen bevat	Behandeling van hemofilie A
Estonian	Sünteetiline kahekeermeline siRNA oligonukleotiid, mis on suunatud antitrombiin mRNA vastu ja mis on kovalentselt seotud kolme N-atsetüülgalaktosamiini jääki sisaldava ligandiga	Hemofiilia A ravi
Finnish	Synteettinen kaksijuosteinen siRNA-oligonukleotidi kohdennettu antitrombiinia mRNA:ta vastaan, joka yhdistyy kovalenttisella sidoksella kolme N-asetyyligalaktosamiinijäämää sisältävään ligandiin	Hemofilia A:n hoito
French	Petit ARN interférent (pARNi) oligonucléotidique synthétique double brin dirigé contre l'ARNm de l'antithrombine, lié de manière covalente à un ligand contenant trois résidus N-acétylgalactosamine	Traitement de l'hémophilie A
German	Synthetisches, doppelsträngiges siRNA Oligonukleotid, gerichtet gegen Antithrombin-mRNA, das kovalent an einen Ligand mit drei N-Acetylgalactosamin-Restgruppen gebunden ist.	Behandlung der Hämophilie A

[1] At the time of designation

Language	Active ingredient	Indication
Greek	Συνθετικό δίκλωνο ολιγονουκλεοτίδιο siRNA κατευθυνόμενο έναντι του RNA αντιθρομβίνης το οποίο συνδέεται ομοιοπολικά με συνδέτη περιέχοντα τρία υπολείμματα N-ακετυλογαλακτοσαμίνης	Θεραπεία της αιμορροφιλίας Α
Hungarian	Az mRNS antitrombin elleni szintetikus kétszálú siRNS oligonukleotid, amely kovalens kötéssel kapcsolódik a három N-acetil-galaktóztamin maradványt tartalmazó ligandumhoz	A típusú hemofília kezelése
Italian	Oligonucleotide siRNA sintetico a doppio filamento diretto contro il mRNA dell'antitrombina legato in modo covalente ad un legante contenente tre residui di N-acetilgalattosamina	Trattamento dell'emofilia A
Latvian	Sintētisks dubultspirāles siRNA oligonukleotīds, kas vērsts pret antitrombīna mRNS un ir kovalenti saistīts ar trīs N-acetilgalaktozamīna atliekas saturošu ligandu	A tipa hemofilijas ārstēšana
Lithuanian	Sintetinis dvigrandis siRNA oligonukleotidas, nukreiptas prieš antitrombiną mRNA ir kovalentiniu ryšiu susietas su ligandu, turinčiu tris N-acetilgalaktozamino liekanas	Hemofilijos A gydymas
Maltese	Oligonukleotide sintetiku tas-siRNA b'katina doppja dirett kontra antithrombin mRNA u magħqud b'mod kovalenti ma' ligand li fih tliet residwi ta' N-acetylgalactosamine	Kura ta' l-emofilja A
Polish	Syntetyczny dwuniciowy oligonukleotyd siRNA skierowany przeciwko antytrombinie mRNA połączony kowalentnie z ligandem zawierającym trzy reszty N-acetylgalaktozaminy	Leczenie hemofilii A
Portuguese	Oligonucleótido sintético siRNA de cadeia dupla dirigido contra o mRNA da antitrombina e com ligação covalente a um ligante contendo três resíduos de N-acetilgalactosamina	Tratamento da hemofilia A
Romanian	Oligonucleotid sintetic siRNA dublu catenar îndreptat împotriva antitrombinei mRNA care este legat covalent de un ligand ce conține trei reziduuri de N-acetil-galactozamină	Tratamentul hemofiliei A
Slovak	Oligonukleotid syntetickej dvojvláknovej siRNA namierený proti mRNA antitrombínu spojený kovalentnou väzbou s ligandom obsahujúcim tri reziduá N-acetylgalaktozamínu	Liečba hemofílie A
Slovenian	Sintetični dvoverižni oligonukleotid siRNA, usmerjen proti mRNA za antitrombin, ki je kovalentno vezan na ligand, ki vsebuje tri preostanke N-acetilgalaktozamina	Zdravljenje hemofilije A
Spanish	Oligonucleótido sintético con ARNip bicatenario dirigido contra el ARNm de la antitrombina, unido covalentemente a un ligando que contiene tres residuos de N-acetilgalactosamina	Tratamiento de la hemofilia A

Language	Active ingredient	Indication
Swedish	Syntetisk dubbelsträngad siRNA-oligonukleotid riktad mot antitrombin-mRNA som är kovalent bunden till en ligand som innehåller tre N-acetylgalaktosaminrester	Behandling av hemofili A
Norwegian	Syntetisk dobbeltrådet siRNA oligonukleotid rettet mot antitrombin mRNA som er kovalent koblet til ligand som inneholder tre N-acetylgalaktosamin residier	Behandling av hemofili A
Icelandic	Tilbúið tvístrengja siRNA ólígónúkleótíð gegn antithrombín mRNA sem er samgilt tengt við bindil sem inniheldur þrjár N-acetýlgalaktósamín leifar.	Meðferð við dreyrasýki A