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Committee for Orphan Medicinal Products

Public summary of opinion on orphan designation

Synthetic double-stranded oligomer specific to the *SERPINA1* gene and containing a cholesterol-conjugated, acyclic nucleobase analogue for the treatment of congenital alpha-1 antitrypsin deficiency

On 11 January 2016, orphan designation (EU/3/15/1605) was granted by the European Commission to Pharma Gateway AB, Sweden, for synthetic double-stranded oligomer specific to the SERPINA1 gene and containing a cholesterol-conjugated, acyclic nucleobase analogue (also known as ARC-AAT) for the treatment of congenital alpha-1 antitrypsin deficiency.

What is congenital alpha-1 antitrypsin deficiency?

Congenital alpha-1 antitrypsin deficiency is an inherited disease characterised by a deficiency of normal forms of a protein called 'alpha-1 proteinase inhibitor' or 'alpha-1 antitrypsin' (AAT).

The liver usually makes AAT. One of the functions of AAT is to protect the lungs from attack by an enzyme called neutrophil elastase. Neutrophil elastase breaks down damaged lung tissue and is produced by white blood cells in response to infection or irritants. In patients lacking AAT, excessive neutrophil elastase activity in the lungs causes destruction of tissue and results in a lung disease called emphysema, which causes symptoms such as shortness of breath, coughing and wheezing. Some forms of the disease can result in accumulation of defective forms of AAT in liver cells, which can cause severe liver cirrhosis (scarring) often requiring liver transplantation.

Congenital AAT deficiency is a debilitating disease that is long lasting and can be life threatening due to the worsening of lung function and lung infections as well as liver injury.

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

At the time of designation, congenital AAT deficiency affected less than 2 in 10,000 people in the European Union (EU). This was equivalent to a total of fewer than 103,000 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 512,900,000 (Eurostat 2015).

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What treatments are available?

At the time of orphan drug designation, AAT, given by infusion (drip) into a vein, was authorised in the EU for treating emphysema caused by congenital AAT deficiency. Patients were also given other medicines to manage the symptoms of obstructive lung disease and help prevent infections of the lungs and the airways.

The sponsor has provided sufficient information to show that the medicine might be of significant benefit for patients with congenital AAT deficiency because of its potential for treating liver injury associated with the disease for which there was no treatment at the time of orphan designation. 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?

Patients with congenital AAT deficiency have a mutation (change) in the *SERPINA1* gene, causing deficiency of AAT and in some cases production of a defective protein. This medicine contains a type of synthetic genetic material which prevents the mutated gene from working. This is expected to reduce the production of defective AAT and thereby reduce the damage to liver cells caused by an accumulation of defective AAT.

The synthetic genetic material in the medicine has been attached to cholesterol (a type of fat) which allows the medicine to be taken up easily into the liver cells. In addition, the medicine contains a second substance, melittin-like peptide, which also helps the medicine to be delivered into the liver cells.

The medicine is not likely to be of benefit to patients with lung injury from congenital AAT 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, clinical trials with the medicine in patients with congenital AAT deficiency were ongoing.

At the time of submission, the medicine was not authorised anywhere in the EU for congenital AAT deficiency. Orphan designation of the medicine had been granted in the US for this condition.

In accordance with Regulation (EC) No 141/2000 of 16 December 1999, the COMP adopted a positive opinion on 10 December 2015 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	Active ingredient	Indication
English	Synthetic double-stranded oligomer specific to the *SERPINA1* gene and containing a cholesterol-conjugated, acyclic nucleobase analogue	Treatment of congenital alpha-1 antitrypsin deficiency
Bulgarian	Синтетичен двойноверижен олигомер, специфичен за гена SERPINA1 и съдържащ конюгиран с холестерол аналог на ациклична нуклеобаза	Лечение на вроден алфа-1 антитрипсинов дефицит
Croatian	Sintetički dvolančani oligomer, specifičan za gen *SERPINA1*, koji sadrži aciklički nukleobazni analog konjugiran kolesterolom	Liječenje prirođenog manjka alfa-1-antitripsina
Czech	Cholesterolem konjugovaný acyklický analog nukleobáze, obsahující syntetický zdvojený oligomer, specifický pro gen SERPINA1	Léčba vrozeném deficitu alfa-1 antitrypsinu
Danish	Syntetisk, dubbelstranget oligomer, der er specifik for SERPINA1-genet og indeholder en kolesterolkonjugeret, acyklisk, nukleobaseanalog.	Behandling af medfødt alfa-1 antitrypsinmangel
Dutch	Synthetisch dubbelstrengs oligomeer specifiek voor SERPINA1 gen en welke een cholesterol-geconjugeerd, acyclisch nucleobaseanaloog bevat	Behandeling van aangeboren alfa-1 antitrypsine deficiëntie
Estonian	SERPINA 1 geeni spetsiifiline sünteetiline kaheahelaline oligomer, mis sisaldab kolesteroolkonjugeeritud atsüklilist nukleoaluse analoogi	Kaasasündinud alfa-1 antitrüpsiini puudulikkuse ravi
Finnish	Synteettinen kaksijuosteinen oligomeeri, joka on spesifinen SERPINA1-geenille sisältäen kolesterikonjugoidun,asyklisen emäsanalogin	Synnynnäisen alfa-1 antitrypsiinin puutteen hoito
French	Oligomère synthétique bicaténaire spécifique du gène SERPINA1 et contenant un analogue de base nucléique acyclique, cholestérol-conjugué	Traitement du déficit congénital en alpha-1 antitrypsine
German	Cholesterin-konjugiertes, azyklisches, Nucleinbasen-Analogon enthaltendes, synthetisches Doppelstrangoligomer, das spezifisch für das SERPINA1-Gen ist	Behandlung von erblichem Alpha-1 Antitrypsinmangel
Greek	Συνθετικό δίκλωνο ολιγομερές ειδικό για το γονίδιο SERPINA1 περιέχον ένα συζευγμένο με χοληστερόλη ακυκλικό ανάλογο νουκλεοβάσης	Θεραπεία της συγγενούς ανεπάρκειας άλφα-1 αντιθρυψίνης
Hungarian	A SERPINA1 génre specifikus, koleszterin-konjugált, aciklikus nukleobázist tartalmazó szintetikus, kettős szálú oligomer	Kongenitális alfa-1 antitripszin hiány kezelése
Italian	Oligomero sintetico a doppia catena coniugato con colesterolo, contenente un analogo aciclico di base azotata, specifico per il gene SERPINA1	Trattamento del deficit congenito di alfa-1 antitripsina

[1] At the time of designation

Language	Active ingredient	Indication
Latvian	Sintētisks *SERPINA1* gēnam specifisks dubultķēdes oligomērs, kas satur ar holesterīnu konjugētu, aciklisku nukleobāzes analogu	Iedzimta alfa -1 antitripsīna deficīta ārstēšana
Lithuanian	Sintetinis dvigrandis oligomeras specifinis *SERPINA1* genui ir turintis konjuguoto cholesterolio, aciklinės nukleobazės analogą	Įgimtas alfa-1 antitripsino deficito gydymas
Maltese	Oligomer sintetiku b'katina doppja speċifiku għall-ġene SERPINA1 li fih analogu ta' acyclic nucleobase ikkonjugat ma' kolesterol	Kura tan-nuqqas konġenitu ta' l-alpha-1 antitrypsin
Polish	Syntetyczny dwuniciowy oligomer swoisty dla genu SERPINA1, zawierajacy acykliczny analog zasady azotowej skoniugowany z cholesterolem	Leczenie wrodzonego niedoboru alfa-1 antytrypsyny
Portuguese	Oligómero sintético de cadeia dupla contendo um análogo de ácido nucleico acíclico, colesterol-conjugado, e específico do gene SERPINA1	Tratamento da deficiência congénita em antitripsina alfa-1
Romanian	Oligomer sintetic dublu catenar, specific genei SERPINA1, care conţine un analog de nucleobază aciclic, conjugat cu colesterol	Tratamentul deficitului congenital de alfa-1 antitripsină
Slovak	Syntetický dvojvláknovný oligomér špecifický pre gén *SERPINA1* a obsahujúci cholesterolom konjugovaný, acyklický nukleobázový analóg	Liečbadeficitu alfa-1 antitrypsínu
Slovenian	Analog aciklične nukleinske baze, konjugiran s holesterolom in vsebujoč sintetičen dvoverižni oligomer, specifičen za gen SERPINA1	Zdravljenje kongenitalnega pomanjkanja alfa-1 antitripsina
Spanish	Oligómero bicatenario sintético del gen SERPINA1 y conteniendo un análogo de nucleobase acíclico conjugado con colesterol.	Tratamiento del déficit congénito de alfa-1 antitripsina
Swedish	Syntetisk dubbelstängad oligomer specific för SERPINA1-genen innehållande en kolesterolkonjugerad acyklisk nukleobasananalog	Behandling av kongenital alpha-1 antitrypsin brist
Norwegian	Tilbúin tvístrengja fálið a sem tengist SERPINA1 geninu og inniheldur kólsteról-tengda raðtengda kjarnabasa afleiðu	Behandling av alfa-1 antitrypsinmangel
Icelandic	Kólesteról-tengd, tilbúin tvístofna fálið a sem tengist SERPINA1 geninu og felur í sér hringlaga núkleóbasahliðstæðu	Meðferð á meðfæddum alfa-1 andtrýpsínskorti