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# Public summary of opinion on orphan designation

## N-acetylgalactosamine-conjugated synthetic double-stranded oligomer specific to serpin family A member 1 gene for the treatment of congenital alpha-1 antitrypsin deficiency

On 31 July 2018, orphan designation (EU/3/18/2048) was granted by the European Commission to Pharma Gateway AB, Sweden, for N-acetylgalactosamine-conjugated synthetic double-stranded oligomer specific to serpin family A member 1 gene (also known as ARO-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 lack 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 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 damages lung tissue and results in emphysema, which causes shortness of breath, coughing and wheezing. Some forms of AAT deficiency can lead to a build-up 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 worsening 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 approximately 2.6 in 10,000 people in the European Union (EU). This was equivalent to a total of around 135,000 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 orphan drug designation, the medicine Respreeza, human alpha1-proteinase inhibitor (AAT), given by infusion (drip) into a vein, was authorised in the EU for slowing down the worsening of 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 laboratory studies show that the medicine can treat the liver damage caused by the condition, 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?

The medicine is intended for use in forms of the disease that cause liver damage. It blocks the gene responsible for the production of defective AAT. This is expected to reduce the production of defective AAT and so reduce damage caused by its build-up in the liver.

## 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 congenital AAT deficiency had been started.

At the time of submission, the medicine was not authorised anywhere in the EU for AAT deficiency. Orphan designation of the medicine had been granted in the United States for AAT deficiency.

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 | N-acetylgalactosamine-conjugated synthetic double-stranded oligomer specific to serpin family A member 1 gene | Treatment of congenital alpha-1 antitrypsin deficiency |
| Bulgarian | Конюгиран с N-ацетилгалактозамин, синтетичен двойноверижен олигомер, специфичен за член 1 ген от семейството на серпини A | Лечение на вроден алфа-1 антитрипсинов дефицит |
| Croatian | Sintetski dvolančani oligomer, specifičan za gen 1 iz skupine serpina A, konjugiran s N-acetilgalaktozaminom. | Liječenje prirođenog manjka alfa-1-antitripsina |
| Czech | Syntetický zdvojený oligomer specifický pro gen člena rodiny serpin A 1 konjugovaný s N-acetylgalaktosaminem | Léčba vrozeném deficitu alfa-1 antitrypsinu |
| Danish | N-acetylgalactosaminkonjugeret, syntetisk dobbeltstrenget oligomer, der er specifik for serpin-familie A medlem 1 | Behandling af medfødt alfa-1 antitrypsinmangel |
| Dutch | N-acetylgalactosamine-geconjugeerd, synthetisch dubbelstrengs oligomeer specifiek voor het gen van lid 1 uit serpinfamilie A | Behandeling van aangeboren alfa-1 antitrypsine deficiëntie |
| Estonian | N-atsetüülgalaktoosamiiniga konjugeeritud serpiin A perekonna 1. liikme geeni spetsiifiline sünteetiline kaheahelaline oligomeer | Kaasasündinud alfa-1 antitrüpsiini puudulikkuse ravi |
| Finnish | N-asetyyligalaktoosiamiinikonjugoitu, synteettinen kaksijuosteinen oligomeeri, joka on spesifinen serpiinien geeniperheen A 1:lle | Synnynnäisen alfa-1 antitrypsiinin puutteen hoito |
| French | Oligomère synthétique bicaténaire, N-acétylgalactosamine-conjugué, spécifique du gène du membre 1 de la famille A des serpines | Traitement du déficit congénital en alpha-1 antitrypsine |
| German | N-Acetylgalactosamin-konjugiertes, synthetisches Doppelstrangoligomer, das spezifisch für Mitglied 1 der Serpin-Genfamilie A ist | Behandlung von erblichem Alpha-1 Antitrypsinmangel |
| Greek | Συζευγμένο με N-ακετυλογαλακτοζαμίνη, συνθετικό δίκλωνο ολιγομερές ειδικό για το γονίδιο του μέλους 1 της οικογένειας A της σερπίνης | Θεραπεία της συγγενούς ανεπάρκειας άλφα-1 αντιθρυψίνης |
| Hungarian | A szerpin „A” család 1-es tagjához tartozó génre specifikus, N-acetilgalaktózamin-konjugált, szintetikus kettős szálú oligomer | Kongenitális alfa-1 antitripszin hiány kezelése |
| Italian | Oligomero sintetico a doppia catena coniugato con N-acetilgalattosamina, specifico per il gene del membro 1 della famiglia A delle serpine | Trattamento del deficit congenito di alfa-1 antitripsina |
| Latvian | Ar N-acetilgalaktozamīnu konjugēts, sintētisks, serpīnu A grupas 1. locekļa gēnam specifisks dubultķēdes oligomērs | Iedzimta alfa -1 antitripsīna deficīta ārstēšana |

[1] At the time of designation

| Language | Active ingredient | Indication |
|---|---|---|
| Lithuanian | N-acetilgalaktozaminas, su specifiniu serpinų šeimos A elemento 1 genu sujungtas sintetiniu dvigrandžiu oligomeru | Įgimtas alfa-1 antitripsino deficito gydymas |
| Maltese | Oligomer sintetiku b'katina doppja speċifiku għall-ġene serpin familja A membru 1, ikkonjugat ma' N-aċetilgalattosamina | Kura tan-nuqqas konġenitu ta' l-alpha-1 antitrypsin |
| Polish | Syntetyczny dwuniciowy oligomer swoisty dla 1 genu należącego do rodziny serpin A, skoniugowany z N-acetylogalaktozaminą. | Leczenie wrodzonego niedoboru alfa-1 antytrypsyny |
| Portuguese | Oligómero sintético de cadeia dupla conjugado com N-acetilgalactosamina, específico do gene do membro 1da família A das serpinas | Tratamento da deficiência congénita em antitripsina alfa-1 |
| Romanian | Oligomer sintetic dublu catenar conjugat cu N-acetilgalactozamină, specific genei membrului 1 din familia A a inhibitorilor de serin-proteaze (serpine) | Tratamentul deficitului congenital de alfa-1 antitripsină |
| Slovak | N-acetylgalaktozamínom konjugovaný syntetický dvojvláknový oligomér špecifický pre gén, ktorý je členom 1 serpinovej skupiny A | Liečba deficitu alfa-1 antitrypsínu |
| Slovenian | Sintetičen dvoverižni oligomer, specifičen za gen 1 serpinske družine A, , konjugiran z N-acetilgalaktozaminom | Zdravljenje kongenitalnega pomanjkanja alfa-1 antitripsina |
| Spanish | Oligómero bicatenario sintético del gen del miembro 1 de la familia A de las serpinas conjugado con N-acetilgalactosamina | Tratamiento del déficit congénito de alfa-1 antitripsina |
| Swedish | N-acetylgalaktosamin-konjugerad, syntetisk dubbelsträngad oligomer specifik för serpinfamilj A medlem 1-genen | Behandling av kongenital alpha-1 antitrypsin brist |
| Norwegian | N-acetylgalaktosamin-konjugert syntetisk dobbeltrådet oligomer spesifikk for serpin familie A medlem 1 genet | Behandling av alfa-1 antitrypsinmangel |
| Icelandic | N-asetýlgalaktósamín-tengd, samtengd tvíþátta fáliða sem er sértæk fyrir serpin gen úr fjölskyldu A 1 | Meðferð á meðfæddum alfa-1 andtrýpsínskorti |