22 June 2017
EMA/272964/2017

# Public summary of opinion on orphan designation

Poly(oxy-1,2-ethanediyl),.alpha.-hydro-.omega.-hydroxy-,15,15'-diester with N-acetyl-L-isoleucyl-L-cysteinyl-L-valyl-1-methyl-L-tryptophyl-L-glutaminyl-L-.alpha.-aspartyl-L-tryptophylglycyl-L-alanyl-L-histidyl-L-arginyl-L-cysteinyl-L-threonyl-2-[2-(2-aminoethoxy)ethoxy]acetyl-N6-carboxy-L-lysinamide cyclic (2.fwdarw.12)-(disulfide); where two identical synthetic peptide domains are covalently linked at the ends of the polyethylene glycol chain for the treatment of paroxysmal nocturnal haemoglobinuria

On 22 May 2017, orphan designation (EU/3/17/1873) was granted by the European Commission to Best Regulatory Consulting Ltd, United Kingdom, for poly(oxy-1,2-ethanediyl),.alpha.-hydro-.omega.-hydroxy-,15,15'-diester with N-acetyl-L-isoleucyl-L-cysteinyl-L-valyl-1-methyl-L-tryptophyl-L-glutaminyl-L-.alpha.-aspartyl-L-tryptophylglycyl-L-alanyl-L-histidyl-L-arginyl-L-cysteinyl-L-threonyl-2-[2-(2-aminoethoxy)ethoxy]acetyl-N6-carboxy-L-lysinamide cyclic (2.fwdarw.12)-(disulfide); where two identical synthetic peptide domains are covalently linked at the ends of the polyethylene glycol chain (also known as APL-2) for the treatment of paroxysmal nocturnal haemoglobinuria.

## What is paroxysmal nocturnal haemoglobinuria?

Paroxysmal nocturnal haemoglobinuria (PNH) is a condition in which there is excessive breakdown of red blood cells (haemolysis), leading to the release into the urine of a large amount of haemoglobin (the protein found in red blood cells that carries oxygen around the body). Because of the red colour of haemoglobin, the passing of red urine, particularly in the mornings, is usually the most obvious sign of the disease. Patients may also experience problems related to blood clotting.

The condition is caused by the lack of certain proteins on the surface of the red blood cells which normally protect them from being destroyed by the immune system (the body's natural defences).

PNH is a long-term debilitating and life-threatening condition due to its complications including abdominal pain, infection and kidney problems, and problems due to bleeding and blood clots.

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

At the time of designation, PNH affected less than 0.1 in 10,000 people in the European Union (EU). This was equivalent to a total of fewer than 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).

## What treatments are available?

At the time of designation, the medicine Soliris (eculizumab) was authorised in the EU for the treatment of PNH. Bone marrow transplantation to replace the defective red blood cells was another therapy available to patients. Other methods such as blood transfusions and treatment with blood-thinning compounds to prevent clotting were used in some patients to improve symptoms.

The sponsor has provided sufficient information to show that the medicine might be of significant benefit for patients with PNH because preliminary data show that the medicine improved haemoglobin levels in patients in whom haemolysis was not controlled by currently authorised treatments. 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 part of the immune system involved in damaging the red blood cells of patients with PNH is called the 'complement system'.

This medicine is made of two synthetic peptides (short chains of amino acids) linked together, which target and attach to an important protein in the complement system called C3. By attaching to C3, the medicine is expected to block the chain of reactions that damage the red blood cells, thus relieving 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 PNH were ongoing.

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

In accordance with Regulation (EC) No 141/2000 of 16 December 1999, the COMP adopted a positive opinion on 11 April 2017 recommending the granting of this designation.

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*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 515,700,000 (Eurostat 2017).

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 | Poly(oxy-1,2-ethanediyl), .alpha.-hydro-.omega.-hydroxy-,15,15'-diester with N-acetyl-L-isoleucyl-L-cysteinyl-L-valyl-1-methyl-L-tryptophyl-L-glutaminyl-L-.alpha.-aspartyl-L-tryptophylglycyl-L-alanyl-L-histidyl-L-arginyl-L-cysteinyl-L-threonyl-2-[2-(2-aminoethoxy)ethoxy]acetyl-N6-carboxy-L-lysinamide cyclic (2.fwdarw.12)-(disulfide); where two identical synthetic peptide domains are covalently linked at the ends of the polyethylene glycol chain | Treatment of paroxysmal nocturnal haemoglobinuria |
| Bulgarian | Поли(окси-1,2-етанедил), .алфа.-хидро-.омега.-хидрокси-,15,15‘-диестер с N-ацетил-L-изолевцил-L-цистеинил-L-валил-1-метил-L-триптофил-L-глутаминил-L-.алфа.-аспартил-L-триптофиглицил-L-аланил-L-хистидил-L-аргинил-L-цистеинил-L-треонил-2-[2-(2-аминоетокси)етокси]ацетил-N6-карбокси-L-лизинамид цикличен (2.fwdarw.12)-(дисулфид); където два идентични синтетични пептидни домейна са ковалентно свързани към краищата на полиетиленгликолова верига | Лечение на пароксизмална нощна хемоглобинурия |
| Croatian | Poli(oksi-1,2-etandiil),.alfa.-hidro-.omega.-hidroksi-,15,15'-diester s N-acetil-L-izoleucil-L-cisteinil-L-valil-1-metil-L-triptofil-L-glutaminil-L-.alfa.-aspartil-L-triptofilglicil-L-alanil-L-histidil-L-arginil-L-cisteinil-L-treonil-2-[2-(2-aminoetoksi)etoksi]acetil-N6-karboksi-L-lisinamid ciklički (2.fvdarv.12)-(disulfid); gdje su dvije identične sintetičke peptidne domene kovelentno vezane na krajevima polietilen glikolnog lanca | Liječenje paroksizmalne noćne hemoglobinurije |
| Czech | Poly(oxy-1,2-ethanediyl), .alpha.-hydro-.omega.-hydroxy-,15,15'-diester with N-acetyl-L-isoleucyl-L-cysteinyl-L-valyl-1-methyl-L-tryptophyl-L-glutaminyl-L-.alpha.-aspartyl-L-tryptophylglycyl-L-alanyl-L-histidyl-L-arginyl-L-cysteinyl-L-threonyl-2-[2-(2-aminoethoxy)ethoxy]acetyl-N6-carboxy-L-lysinamide cyclic (2.fwdarw.12)-(disulfide); kde dvě identické syntetické peptidové domény jsou kovalentně navázány ke koncům řetězce polyethylene glykolu | K léčbě paroxysmální noční hemoglobinurie |
| Danish | Poly(oxy-1,2-ethanediyl), .alpha.-hydro-.omega.-hydroxy-,15,15'-diester med N-acetyl-L-isoleucyl-L-cysteinyl-L-valyl-1-methyl-L-tryptophyl-L-glutaminyl-L-.alpha.-aspartyl-L-tryptophylglycyl-L-alanyl-L-histidyl-L-arginyl-L-cysteinyl-L-threonyl-2-[2-(2-aminoethoxy)ethoxy]acetyl-N6-carboxy-L-lysinamid cyclisk (2.fwdarw.12)-(disulfid); hvor to identiske syntetiske peptiddomæner er kovalent bundet ved enderne af polyethylenglycol kæden. | Behandling af paroksysmatisk nocturn hæmoglobinuria |

[1] At the time of designation

| Language | Active ingredient | Indication |
|---|---|---|
| Dutch | Poly(oxy-1,2-ethanediyl), .alpha.-hydro-.omega.-hydroxy-,15,15'-diester with N-acetyl-L-isoleucyl-L-cysteinyl-L-valyl-1-methyl-L-tryptophyl-L-glutaminyl-L-.alpha.-aspartyl-L-tryptophylglycyl-L-alanyl-L-histidyl-L-arginyl-L-cysteinyl-L-threonyl-2-[2-(2-aminoethoxy)ethoxy]acetyl-N6-carboxy-L-lysinamide cyclisch (2.fwdarw.12)-(disulfide); waarbij twee identieke synthetische peptidedomeinen covalent gebonden zijn aan de einden van de polyethyleenglycolketen | Behandeling van paroxismale nachtelijke hemoglobinurie |
| Estonian | Polü(oksü-1,2-etanediüül), .alfa.-hydro-.omega.-hüdroksü-,15,15'-diester koos N-atsetüül-L-isoleutsüül-L-tsüsteinüül-L-valüül-1-metüül-L-trüptofüül-L-glutaminüül-L-.alfa.-aspartüül-L-trüptofüülglütsüül-L-alanüül-L-histidüül-L-arginüül-L-tsüteinüül-L-treonüül-2-[2-(2-aminoetoksü)ethxü]atsetüül-N6-karboksü-L-lüsinamiid tsüklik (2.fwdarw.12)-(disulfiid); kus kaks identset sünteetilise peptiidi domeeni on kovalentselt ühendatud polüetüleenglükooli ahela  lõpus | Paroksüsmaalse öise hemoglubinuuria ravi |
| Finnish | Poly(oksi-1,2-etanediyyli), .alfa.-hydro-.omega.-hydroksi-,15,15'-diesteri yhdessä N-asetyyli-L-isoleusyyli-L-kysteinyyli-L-valyyli-1-metyyli-L-tryptofyyli-L-glutaminyyli-L-.alpha.-aspartyyli-L-tryptofyyliglysyyli-L-alanyyli-L-histidyyli-L-arginyyli-L-kysteinyyli-L-threonyyli-2-[2-(2-aminoetoksi)etoksi]asetyyli-N6-karboksi-L-lysinamidi syklinen (2.fwdarw.12)-(disulfidi); jossa kaksi identtistä, synteettistä peptidi domeeinia on kovalentisti yhdistettynä polyetyleeniglykoliketjun päihin | Paroksysmaalisen nokturnaalisen hemoglobinurian hoito |
| French | Poly(oxy-1,2-ethanediyl), .alpha.-hydro-.omega.-hydroxy-,15,15'-diester avec N-acetyl-L-isoleucyl-L-cysteinyl-L-valyl-1-methyl-L-tryptophyl-L-glutaminyl-L-.alpha.-aspartyl-L-tryptophylglycyl-L-alanyl-L-histidyl-L-arginyl-L-cysteinyl-L-threonyl-2-[2-(2-aminoethoxy)ethoxy]acetyl-N6-carboxy-L-lysinamide cyclic (2.fwdarw.12)-(disulfide); avec deux domaines de peptides synthetiques identiques lies de maniere covalente a la fin de la chaine the polyethylene glycol. | Traitement de l'hémoglobinurie paroxystique nocturne |
| German | Poly(oxy-1,2-ethanediyl), .alpha.-hydro-.omega.-hydroxy-,15,15'-diester with N-acetyl-L-isoleucyl-L-cysteinyl-L-valyl-1-methyl-L-tryptophyl-L-glutaminyl-L-.alpha.-aspartyl-L-tryptophylglycyl-L-alanyl-L-histidyl-L-arginyl-L-cysteinyl-L-threonyl-2-[2-(2-aminoethoxy)ethoxy]acetyl-N6-carboxy-L-lysinamide cyclic (2.fwdarw.12)-(disulfide); zwei identische syntetische Peptid-Domänen die am Ende der Polyethylen-Glycol Kette kovalent miteinander verbunden sind | Behandlung von paroxysmaler nächtlicher Hämoglobinurie |

| Language | Active ingredient | Indication |
|---|---|---|
| Greek | Πολυ(οξυ-1,2-αιθανεδιυλ), .α.-υδρο-.ω.-υδροξυ-,15,15'-διεστέρας με N-ακτευλ-L-ισολευκυλ-L-κυστεινυλ-L-βαλυλ-1-μεθυλ-L-τρυπτοφυλ-L-γλουταμινυλ-L-.α.-ασπαρτυλ-L-τρυπτοφυλγλυκυλ-L-αλανυλ-L-ιστιδυλ-L-αργινυλ-L-κυστεϊνυλ-L-θρεονυλ-2-[2-(2-αμινοαιθοξυ)αιθοξυ]ακετυλ -N6-καρβοξυ-L-λυσιναμίδιο κυκλικό (2.fwdarw.12)-(δισουλφίδιο); με δύο ίδια τμήματα συνθετικών πεπτιδίων ομοιπολικά συνδεμένα στα άκρα μιας αλυσίδας πολυαιθυλενογλυκόλης | Θεραπεία της παροξυσμικής νυκτερινής αιμοσφαιρινουρίας |
| Hungarian | Poli(oxy-1,2-ethanediyl), .alpha.-hydro-.omega.-hydroxy-,15,15'-diészter; N-acetyl-L-isoleucyl-L-cysteinyl-L-valyl-1-methyl-L-tryptophyl-L-glutaminyl-L-.alpha.-aspartyl-L-tryptophylglycyl-L-alanyl-L-histidyl-L-arginyl-L-cysteinyl-L-threonyl-2-[2-(2-aminoethoxy)ethoxy]acetyl-N6-carboxy-L-lysinamid ciklikus (2.fwdarw.12)-(diszulfid)-dal; ahol két azonos szintetikus peptid domén kovalens kötéssel kapcsolódik a polietilén-glikol lánc végein | Paroxysmalis nocturnalis haemoglobinuria kezelése |
| Italian | Poli(oxi-1,2-etanedil), .alfa.-idro-.omega.-idroxy-,15,15'-diester con N-acetil-L-isoleucil-L-cisteinil-L-valil-1-metil-L-triptofil-L-glutaminil-L-.alfa.-aspartil-L-triptofilglicil-L-alanil-L-histidil-L-arginil-L-cysteinil-L-treonil-2-[2-(2-aminoetossi)etossi]acetil-N6-carbossi-L-lisinamide ciclica (2.fwdarw.12)-(disulfide); due identici domini peptidici sintetici covalentemente legati ai terminali della catena di polietilene glicolico. | Trattamento dell'emoglobinuria parossistica notturna |
| Latvian | Poli(oksi-1,2-etānediil), .alfa.-hidro-.omega.-hidroksi-,15,15'-diesters ar N-acetil-L-izoleicil-L-cisteinil-L-valil-1-metil-L-triptofil-L-glutaminil-L-.alfa.-aspartil-L-triptofilglicil-L-alanil-L-histidil-L-arginil-L-cisteinil-L-treonil-2-[2-(2-aminoetoksi)etoksi]acetil-N6-karboksi-L-lizīnamīda ciklisks (2.fwdarw.12)-(disulfīds); kurā divi identiski sintētiska peptīda domēni ir kovalenti saistīti poietilēnglikola ķēdes galos | Paroksismālas nakts hemoglobinūrijas ārstēšana |
| Lithuanian | Poli(oksi-1,2-etanedil), .alfa.-hidro-.omega.-hidroksi-,15,15'-diesteris su N-acetil-L-izoleucil-L-cisteinil-L-valil-1-metil-L-triptofil-L-glutaminil-L-.alfa.-aspartil-L-triptofilglicil-L-alanil-L-histidil-L-arginil-L-cisteinil-L-treonil-2-[2-(2-aminoetoksi)etoksi]acetil-N6-karboksi-L-lizinamido ciklinis (2.fwdraw.12)-(disulfidas); kur du identiškų sintetinių peptidų domenai yra kovalentiškai susijungę galais su polietileno glikolio seka | Priepuolinės naktinės hemoglobinurijos gydymas |

| Language | Active ingredient | Indication |
|---|---|---|
| Maltese | Poli(ossi-1,2-etanedil), .alfa.-idro-.omega.-idrossi-,15,15'-diester bi N-aċetil-L-isolewċil-L-ċisteinil-L-valil-1-metil-L-triptofil-L-glutaminil-L-.alfa.-aspartil-L-triptofilgliċil-L-alanil-L-istidil-L-arginil-L-ċisteinil-L-treonil-2-[2-(2-aminoetossi)etossi]aċetil-N6-karbossi-L-lisinamur ċikliku (2.fwdarw.12)-(disulfur); fejn żewġ dominji ta' peptidi sintetiċi identiċi jkunu marbutin b'mod kovalenti fit-trufijiet tal-katina tal-glikol tal-polietilen | Kura ta' l-emoglobinurja parossistika ta' billejl |
| Polish | Poli(oksy-1,2-etanodiylo), .alfa.-hydro-.omega.-hydroksy-,15,15'-diester oraz N-acetylo-L-isoleucylo-L-cysteinylo-L-walylo-1-metylo-L-tryptofylo-L-glutaminylo-L-.alfa.-aspartylo-L-tryptofylglicylo-L-alanylo-L-histidylo-L-arginylo-L-cysteinylo-L-treonylo-2-[2-(2-aminoetoksy)etoksy]acetylo-N6-karboksy-L-lysinamid cykliczny (2.fwdarw.12)-(disulfid); gdzie dwie identyczne syntetyczne domeny peptydowe są kowalentnie połączone na końcach łańcuchem glikolu polietylenowego | Leczenie napadowej nocnej hemoglobinurii |
| Portuguese | (1R,3R,4R,5S)-3-({2-N-acetilamino-2-desoxi-3-O-[(1S)-1-carboxilato-2-ciclo-hexiletilol]-beta-D-galactopiranosil}oxi)-4-({6-desoxi-alfa-L-galactopiranosil}oxi)-5-etil-ciclo-hexan-1-il-(38-oxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-39-aza-hentetracontan-41-il) carboxamida sódica | Tratamento da hemoglobinúria paroxística nocturna |
| Romanian | Poli(oxi-1,2-etanediil), .alfa.-hidro-.omega.-hidroxi-,15,15'-diester cu N-acetil-L-izoleucil-L-cisteinil-L-valil-1-metil-L-triptofil-L-glutaminil-L-.alfa.-aspartil-L-triptofilglicil-L-alanil-L-histidil-L-arginil-L-cisteinil-L-treonil-2-[2-(2-aminoetoxi)etoxi]acetil-N6-carboxi-L-lizinamidă ciclică (2.fwdarw.12)-(disulfid); cu două domenii peptidice sintetice identice legate covalent la sfârşitul catenei de polietilenglicol. | Tratamentul hemoglobinuriei paroxistice nocturne |
| Slovak | Poly(oxy-1,2-etánediyl), .alfa.-hydro-.omega.-hydroxy-,15,15'-diester s N-acetyl-L-izoleucyl-L-cysteinyl-L-valyl-1-metyl-L-tryptofyl-L-glutaminyl-L-.alfa.-aspartyl-L-tryptofylglycyl-L-alanyl-L-histidyl-L-arginyl-L-cysteinyl-L-threonyl-2-[2-(2-aminoetoxy)etoxy]acetyl-N6-karboxy-L-lyzínamid cyklický (2.fwdarw.12)-(disulfid); kde dve identické syntetické peptidové domény sú kovalentne spojené na koncoch polyetylénglykolového reťazca | Liečba paroxyzmálnej nočnej hemoglobinúrie |
| Slovenian | Poli(oksi-1,2-etandiil), .alfa.-hidro-.omega.-hidroksi-,15,15'-diester with N-acetil-L-izolevcil-L-cisteinil-L-valil-1-metil-L-triptofil-L-glutaminil-L-.alpha.-aspartil-L-triptofylglicil-L-alanil-L-histidil-L-arginil-L-cisteinil-L-treonil-2-[2-(2-aminoetoksi)ethoksi]acetil-N6-karboksi-L-lizinamide ciclični (2.fwdarw.12)-(disulfid); kjer sta dve identični sintetični peptidni domeni kovalentno vezani na konec polietilenglikolne verige | Zdravljenje paroksizmalne nočne hemoglobinurije |

| Language | Active ingredient | Indication |
|---|---|---|
| Spanish | Poli(oxi-1,2-etanedil), .alfa.-hidro-.omega.-hidroxi-,15,15'-diester con N-acetil-L-isoleucil-L-cistenil-L-valil-1-metil-L-tryptofil-L-glutaminil-L-.alfa.-aspartil-L-triptofilglicil-L-alanil-L-histidil-L-arginil-L-cisteinil-L-treonil-2-[2-(2-aminoetoxi)etoxi]acetil-N6-carboxi-L-lisinamide ciclico (2.fwdarw.12)-(disulfide); donde dos dominos de peptide sintetic estan vinculados covantentemente a los terminals de la cadena de polietilena glycol | Tratamiento de la hemoglobinuria paroxística nocturna |
| Swedish | Poly(oxi-1,2-etandiyl), .alfa.-hydro-.omega.-hydroxi-,15,15'-diester med N-acetyl-L-isoleucyl-L-cysteinyl-L-valyl-1-metyl-L-tryptofyl-L-glutaminyl-L-.alfa.-aspartyl-L-tryptofylglycyl-L-alanyl-L-histidyl-L-arginyl-L-cysteinyl-L-treonyl-2-[2-(2-aminoetoxi)etoxi]acetyl-N6-karboxy-L-lysinamid cyklisk (2.fwdarw.12)-(disulfid); där två identiska syntetiska peptiddomäner är kovalent kopplade till ändarna av polyetylenglykolkedjan | Behandling av paroxysmal nattlig hemoglobinuri |
| Norwegian | Poly(oksy-1,2-etandiyl), .alpha.-hydro-.omega.-hydroksy-,15,15'-diester med N-acetyl-L-isoleucyl-L-cysteinyl-L-valyl-1-metyl-L-tryptofyl-L-glutaminyl-L-.alpha.-aspartyl-L-tryptofylglysyl-L-alanyl-L-histidyl-L-arginyl-L-cysteinyl-L-treonyl-2-[2-(2-aminoetoksy)etoksy]acetyl-N6-karboksy-L-lysinamid syklisk (2.fwdarw.12)-(disulfid); der to identiske syntetiske peptiddomener er kovalent bundet til endene av polyetylenglykolkjeden | Behandling av paroksysmal nattlig hemoglobinuri |
| Icelandic | Pólýoxý-1,2-ethanedýl), alfa-hýdró-,ómega,-hýdroxý-,15 díester með N-acetýl-L-ísóleusýl-L-cýsteinýl-L-valýl-1-metýl-Ltrýptóphýl-L glútamínýl-L-alfa-aspartýl-L-trýptóphýlglýcýl-L-alanýl-histidýl-arginýl-L cýstenýl-L-threónýl -2-[2-(2 amínóetoxý] acetyl-N6-karboxý-L-lípínamíð c´klík (2. Fwdarw. 1.2)-dísúlfíð); þar sem tvö eins tilbúin peptíð svæði eru kóvalent tengd við enda pólýethýlen glýkól keðjuna | Meðferð fyrir paroxysmal nætur blóðrauðamigu |