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HEALTH TECHNOLOGY BRIEFING
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Ravulizumab for paroxysmal nocturnal haemoglobinuria in paediatrics

NIHRIO ID	28894	**NICE ID**	10514
Developer/Company	Alexion Pharmaceuticals Inc	**UKPS ID**	N/A

Licensing and market availability plans	Currently in phase III clinical trial.

SUMMARY

Ravulizumab is in clinical development for the treatment of paediatric patients with paroxysmal nocturnal hemoglobinuria (PNH). PNH is a rare blood condition in which red blood cells are attacked by the body's immune system. PNH is a chronic condition that is associated with complications that can be severely debilitating and life-threatening including abdominal pain, kidney problems, fatigue, shortness of breath, bleeding and blood clots, dysphagia, organ damage and premature mortality.

Ravulizumab, administered intravenously, works by attaching to the complement component 5 (C5) protein, which is part of the complement system (a component of the immune system). By attaching to the C5 protein, ravulizumab blocks its effect and thereby reduces the destruction of red blood cells. If licensed, ravulizumab will provide a treatment option for paediatric patients with PNH.

PROPOSED INDICATION

Treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH):[a]
- in patients with haemolysis with clinical symptom(s) indicative of high disease activity
- in patients who are clinically stable after having been treated with eculizumab for at least the past 6 months.

TECHNOLOGY

DESCRIPTION

Ravulizumab (ALXN1210) is a monoclonal antibody $IgG_{2/4K}$ that specifically binds to the C5 molecule, thereby inhibiting its cleavage to C5a (the proinflammatory anaphylatoxin) and C5b (the initiating subunit of the terminal complement complex [C5b-9]) and preventing the generation of C5b-9. Ravulizumab preserves the early components of complement activation that are essential for opsonisation of microorganisms and clearance of immune complexes.[1]

Ravulizumab is in clinical development for the treatment of paediatric patients with PNH. In the phase III clinical trial (NCT03406507), patients received dosages based on their body weight. Patients received a loading dose of ravulizumab, on day 1, followed by first maintenance treatment dose on day 15 and subsequent maintenance treatment doses every 8 weeks (q8w) thereafter for patients weighing ⩾ 20 kg, or once every 4 weeks (q4w) for patients weighing < 20 kg.[a]

INNOVATION AND/OR ADVANTAGES

Ravulizumab is a long-acting, second-generation C5 inhibitor that is administered intravenously every 8 weeks. Current clinical management for adults and children with PNH includes treatment with the complement inhibitor, eculizumab, which needs to be administered very 2 weeks. Ravulizumab was designed to alleviate the burden of the eculizumab treatment schedule and to reduce the frequency of breakthrough haemolysis. In two phase 3 trial, ravulizumab was safe and effective in patients who were naïve to complement inhibitor treatments and in patients who were clinically stable on eculizumab treatment.[2] However, the safety and efficacy of ravulizumab in children with PNH aged 0 to < 18 years have not been established.[3]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Ravulizumab currently has Marketing Authorisation in the EU/UK for the following indications:[1]
- Treatment of adult patients with PNH:
  - in patients with haemolysis with clinical symptom(s) indicative of high disease activity.
  - in patients who are clinically stable after having been treated with eculizumab for at least the past 6 months

[a] Information provided by Alexion Pharmaceutical Inc

- Treatment of patients with a bodyweight of 10 kg or above with atypical haemolytic uremic syndrome (aHUS) who are complement inhibitor treatment-naïve or have received eculizumab for at least 3 months and have evidence of response to eculizumab.

The most common side effects with ravulizumab (which may affect more than 1 in 10 people) are upper respiratory tract infection (nose and throat infection), nasopharyngitis (inflammation of the nose and throat) and headache. The most serious side effect is meningococcal infection, a bacterial infection caused by neisseria meningitidis that can cause meningitis and blood poisoning.[4]

Ravulizumab is in phase III clinical development for various indications of PNH, COVID-19 (including acute lung injury, acute respiratory distress syndrome and viral pneumonia), thrombotic microangiopathies, acute kidney injury, neuromyelitis optica spectrum disorder, generalized myasthenia gravis, amyotrophic lateral sclerosis and aHUS.[5]

PATIENT GROUP

DISEASE BACKGROUND

PNH is a rare blood condition in which there is excessive breakdown of red blood cells (haemolysis), leading to the release of a large amount of haemoglobin into the urine (the protein found in red blood cells that carries oxygen around the body).[4] PNH is a chronic condition that is associated with complications that can be severely debilitating and life threatening including abdominal pain, kidney problems, fatigue, shortness of breath, bleeding and blood clots, dysphagia, organ damage and premature mortality.

PNH occurs when mutations of a gene called phosphatidylinositol N-acetylglucosaminyltransferase subunit A (PIG-A) occur in a bone marrow stem cell. Stem cells give rise to all the mature blood elements including red blood cells, which carry oxygen to the tissues; white blood cells, which fight infection; and platelets, which are involved in forming blood clots. In PNH, the affected stem cell passes the PIG-A mutation to all cells derived from the abnormal stem cell. Cells harbouring PIG-A mutations are deficient in a class of proteins called glycosylphosphatidylinisotol (GPI)-anchored proteins. Certain GPI-anchored proteins protect red blood cells from destruction, some are involved in blood clotting, and others are involved in fighting infection.[6]

The absence of GPI-anchored proteins on PNH erythrocytes renders them susceptible to terminal complement-mediated haemolysis. Haemolysis most likely contributes to thromboembolism (TE) in PNH. TE is the leading cause of mortality in patients with PNH, and an initial thrombotic event increases the relative risk of death in PNH 5- to 10-fold.[7] The most common complication of PNH is venous or arterial thrombosis. Thrombosis occurs in approximately half of patients with haemolytic PNH and is the cause of death in a third of patients. Approximately 10% of patients present with thrombosis as the first manifestation of their PNH.[8]

There can be a marked variation in the signs and symptoms observed due to PNH both between patients and in the same patient at different times. Common symptoms include

haemoglobinuria, anaemia, breathlessness, difficulty swallowing and abdominal pain, erectile dysfunction, fatigue, jaundice, kidney damage and blood clots.[9]

Renal failure is extremely common in PNH and has been reported to contribute to between 8% and 18% of the deaths due to the disease. PNH often affects young adults (although it is seen in all ages) which usually persists for the remainder of the patient's life and results in the death of approximately half of sufferers if untreated.[8]

CLINICAL NEED AND BURDEN OF DISEASE

Although PNH has been described worldwide, exact prevalence data are not available.[10] In 2017, PNH affected less than 0.1 in 10,000 people in the European Union (EU).[4] An incidence estimate of about 1 per 770,000 per year has been reported with a predicted prevalence of approximately 1 per 62,500 in in Great Britain.[10] Using the 2017-2018 population estimates, there are approximately 1038 people with PNH in Great Britain.[11]

According to the Highly Specialised Services Highlight Report 2016/17 by NHS England, about 650 people in England suffer from PNH.[12]

According to HES data for England, in 2019-20 there were 576 finished consultant episodes (FCE), resulting in 554 admissions, 491 day cases and 299 FCE bed days due to PNH (ICD-10 code: D59.5).[13]

PNH can occur at any age but is most frequently diagnosed between the ages of 30-40 years old. Ten-year survival has been estimated to range between 65% and 78%.[14]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

The PNH Education and Study group (PESG) report that PNH treatment can be grouped under three headings:[15]

- Supportive treatments and immunosuppressive treatments
- Treatment changing the course of the disease
- Potential curative treatment

Currently, allogeneic bone marrow transplantation is the only potential curative treatment option for PNH.[15]

CURRENT TREATMENT OPTIONS

According to the PESG, supportive treatments and immunosuppressive treatments include: [15]

- Blood/erythrocyte suspension transfusion
- Oral iron supplementation
- Steroids
- Anticoagulant treatment
- Immunosuppressive treatment

Treatment changing the course of the disease include:[15]

- Eculizumab to reduce the risk of organ damages in PNH. Patients should be vaccinated against meningococcus at least 2 weeks before initiating eculizumab treatment to reduce the risk of meningococcal infection.

Potential curative treatment:[15]

- Allogeneic bone marrow transplantation

PLACE OF TECHNOLOGY

If licenced, ravulizumab will provide a treatment option for paediatric patients with PNH.

CLINICAL TRIAL INFORMATION

Trial	**NCT03406507, EudraCT 2017-002820-26; A Phase 3, Open-Label Study of ALXN1210 in Children and Adolescents with Paroxysmal Nocturnal Hemoglobinuria (PNH)** **Trial phase III** – Recruiting **Location(s):** EU (Incl UK), USA and Russia **Primary completion date:** June 2021
Trial design	Single group assignment, open-label
Population	N=13 (planned); aged <18 years, weighing ≥ 5 kg; PNH; presence of 1 or more of the following PNH-related signs or symptoms within 3 months of screening; LDH level ≥ 1.5 × ULN for patients not being treated with eculizumab at screening and LDH level ≤ 1.5 × ULN for patients taking eculizumab
Intervention(s)	Ravulizumab • Single loading dose on day 1, followed by regular maintenance dosing beginning on day 15, based on weight
Comparator(s)	No comparator
Outcome(s)	• Maximum serum concentration (pharmacokinetic parameter) (Time frame: Baseline, week 2, 10, 18, and 26) • Trough serum concentration (pharmacokinetic parameter) (Time frame: Baseline, week 2, 10, 18, and 26) • Accumulation ratio (pharmacokinetic parameter) (Time frame: Baseline, week 2, 10, 18, and 26)

	• Free C5 concentrations (pharmacodynamic parameter) (Time frame: Baseline, week 2, 10, 18, and 26) • Change in chicken red blood cell (pharmacodynamic parameter) (Time frame: Baseline, week 2, 10, 18, and 26) See trial record for the full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

ESTIMATED COST

The cost of ravulizumab is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Ravulizumab for treating paroxysmal nocturnal haemoglobinuria. [GID-TA10690]. Estimated publication date: To be confirmed

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Paroxysmal Nocturnal Haemoglobinuria Service Adults and Adolescents. B05/S(HSS)/a.

OTHER GUIDANCE

- PNH Education and Study Group. Pesg PNH diagnosis, follow-up and treatment guidelines. 2016.[15]

ADDITIONAL INFORMATION

Alexion Pharmaceuticals Inc. did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

REFERENCES

1 Electronic Medicines Compendium (emc). *Ultomiris 1,100 mg/11 mL concentrate for solution for infusion.* Available from: https://www.medicines.org.uk/emc/product/11945/smpc#PHARMACODYNAMIC_PROPS [Accessed 14 December 2020].

2 Lee JW, Kulasekararaj AG. Ravulizumab for the treatment of paroxysmal nocturnal hemoglobinuria. *Expert Opin Biol Ther*. 2020 Mar;20(3):227-37. Available from: https://doi.org/10.1080/14712598.2020.1725468.

3 European Medicine Agency (EMA). *Summary of Product Characteristics.* Available from: https://www.ema.europa.eu/en/documents/product-information/ultomiris-epar-product-information_en.pdf [Accessed 14 December 2020].

4 European Medicines Agency. *EU/3/17/1873.* Available from: https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu3171873 [Accessed 14 December 2020].

5 Clinicaltrials.gov. *Ravulizumab | Phase 3.* Available from: https://www.clinicaltrials.gov/ct2/results?term=ravulizumab&age_v=&gndr=&type=&rslt=&phase=2&Search=Apply [Accessed 14 December 2020].

6 Johns Hopkins Medicine. *Paroxysmal Nocturnal Hemoglobinuria (PNH).* 2019. Available from: https://www.hopkinsmedicine.org/kimmel_cancer_center/types_cancer/paroxysmal_nocturnal_hemoglobinuria_PNH.html [Accessed 14 December 2020].

7 Hillmen P, Muus P, Dührsen U, Risitano AM, Schubert J, Luzzatto L, et al. Effect of the complement inhibitor eculizumab on thromboembolism in patients with paroxysmal nocturnal hemoglobinuria. *Blood*. 2007;110(12):4123-8. Available from: https://doi.org/10.1182/blood-2007-06-095646.

8 NHS England. *2013/14 NHS Standard Contract for Paroxysmal Nocturnal Haemoglobinuria Service (Adults and Adolescents).* 2013. Available from: https://www.england.nhs.uk/wp-content/uploads/2013/06/b05-parox-haem-serv.pdf [Accessed 14 December 2020].

9 PNH National Service. *Signs and Symptoms.* 2019. Available from: http://www.pnhleeds.co.uk/patients/what-is-pnh/signs-and-symptoms/ [Accessed 14 December 2020].

10 Orphanet. *Paroxysmal nocturnal hemoglobinuria.* 2019. Available from: https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=GB&Expert=447 [Accessed 14 December 2020].

11 Office of National Statistics. *Estimates of the population for the UK, England and Wales, Scotland and Northern Ireland.* 2018. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/datasets/populationestimatesforukenglandandwalesscotlandandnorthernireland [Accessed 14 December 2020].

12 NHS England. *Highly Specialised Services Highlight Report 2016/17.* 2017. Available from: https://www.england.nhs.uk/wp-content/uploads/2018/03/highly-specialised-services-17.pdf [Accessed 14 December 2020].

13 NHS Digital. *Hospital Admitted Patient Care Activity, 2018-19.* 2019. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2019-20 [Accessed 02 January 2021].

14 National Institute for Health and Care Excellence. *Proposed Highly Specialised Technologies Evaluation: Ravulizumab for treating paroxysmal nocturnal haemoglobinuria.* Available from: https://www.nice.org.uk/guidance/gid-ta10690/documents/draft-scope-pre-referral-3 [Accessed 14 December 2020].

15 Sahin F, Akay OM, Ayer M, Dal MS, Ertop S, Ilhan O, et al. Pesg PNH diagnosis, follow-up and treatment guidelines. *American journal of blood research*. 2016;6(2):19. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4981648/.

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