

EVIDENCE BRIEFING
August 2018

**Ravulizumab for atypical haemolytic uraemic
syndrome in adults and children – first line**

NIHRI ID	13606	NICE ID	9924
Developer/Company	Alexion Pharmaceuticals Inc	UKPS ID	648354

Licensing and market availability plans	Currently in phase III clinical trials
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SUMMARY

Ravulizumab is a medicinal product that is being developed for the treatment of atypical haemolytic uraemic syndrome (aHUS) in adults and children. aHUS is an ultra-rare disease caused by a fault in part of the body’s immune response, called the complement system. This fault causes the complement system to attack the body’s own cells, especially those that line the blood vessels. This leads to clots forming within the small vessels and eventually serious medical problems such as kidney failure which, in most cases, progress to end stage kidney failure. aHUS occurs in childhood more frequently than in adulthood. It often results from a combination of environmental and genetic factors. Faults (mutations) in some genes increase the risk of developing aHUS.

Ravulizumab works by inhibiting a component in the complement system called C5. It is given intravenously and has the potential to increase patient’s quality of life and to decrease treatment burden due to its extended effect that enables every 8-week dosing. If licensed, ravulizumab will offer an additional first-line treatment option for adults and children with aHUS.

PROPOSED INDICATION

Atypical haemolytic uraemic syndrome (aHUS) in adults and children – first line^a

TECHNOLOGY

DESCRIPTION

Ravulizumab (ALXN1210) is a long-acting anti-complement Component 5 (C5) monoclonal antibody that works by inhibiting the C5 protein in the terminal complement cascade, a part of the body's immune system that, when activated in an uncontrolled manner, plays a role in severe ultra-rare disorders such as atypical haemolytic uraemic syndrome (aHUS).^{1,2,3}

In the phase III clinical trial (NCT02949128),⁴ ravulizumab is given intravenously (IV)⁵ as a single loading dose on day 1, followed by regular maintenance dosing beginning on day 15, based on weight as follows:

- ≥ 40 to <60 kg: 2400 mg loading, then 3000 mg every 8 weeks
- ≥ 60 to <100 kg: 2700 mg loading, then 3300 mg every 8 weeks
- ≥100 kg: 3000 mg loading, then 3600 mg every 8 weeks.⁴

INNOVATION AND/OR ADVANTAGES

Ravulizumab is a longer-acting anti-C5 monoclonal antibody than the currently available C5 monoclonal antibody eculizumab. Ravulizumab has demonstrated immediate, complete, and sustained C5 inhibition, with a terminal half-life about 4-fold longer than eculizumab.² In patients with paroxysmal nocturnal haemoglobinuria (PNH), studies have shown that ravulizumab demonstrated non-inferiority to the current treatment option, eculizumab, with all endpoints favoring ravulizumab.⁶ Furthermore, ravulizumab has the potential to decrease treatment burden as it is administered every 8 weeks whereas the current treatment option is given intravenously once every 2 weeks as a maintenance therapy.^{18,7}

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Ravulizumab is not currently licensed for any indication in the UK.^{8,9}

A paediatric investigational plan was agreed in 2017 by the EMA for ravulizumab in aHUS (PIP number: EMEA-001943-PIP01-16) in the EU.¹⁰

Ravulizumab is currently in clinical trials at phase III of development for aHUS and for paroxysmal nocturnal haemoglobinuria (PNH).¹¹ Phase III trials in PNH have completed and applications have been submitted in the US and EU.^{7,12}

^a Information from UK PharmaScan

PATIENT GROUP

DISEASE BACKGROUND

Atypical haemolytic uraemic syndrome (aHUS) is an extremely rare disease characterized by low levels of circulating red blood cells due to their destruction (haemolytic anaemia), low platelet count (thrombocytopenia) due to their consumption and inability of the kidneys to process waste products from the blood and excrete them into the urine (acute kidney failure), a condition known as uraemia.¹³

aHUS is caused by a fault in the complement system. The complement system is part of the body's immune response. This is a group of proteins that work together to destroy foreign invaders (such as bacteria and viruses), trigger inflammation, and remove debris from cells and tissues. The body has an in-built system of protector proteins that stop complement from attacking its own cells. In aHUS, complement starts to attack the body's own cells, especially those that line the blood vessels. This leads to clots forming within the small vessels. The most commonly affected organ is the kidney but all organs can be affected. These clots can cause serious medical problems if they restrict or block blood flow, including haemolytic anaemia, thrombocytopenia, and kidney failure. If left untreated, it can be a life-threatening illness and the majority of people would develop end stage kidney failure.^{14,15,16}

aHUS is a complex disorder and multiple factors, including certain genetic, environmental and immunologic factors, all play a role in its development.¹³ Mutations, in at least seven genes, appear to increase the risk of developing the disorder.¹⁶ A genetic fault in the complement system or the protector proteins causes complement to target the body's own cells. Some patients may also develop autoantibodies to the protector proteins. These autoantibodies then stop the protector protein from doing its job.¹⁴

Although gene mutations increase the risk of aHUS, studies suggest that they are often not sufficient to cause the disease. In people with certain genetic changes, the signs and symptoms of the disorder may be triggered by factors including certain medications (such as anticancer drugs), chronic diseases, viral or bacterial infections, cancers, organ transplantation, or pregnancy. Some people with aHUS do not have any known genetic changes or environmental triggers for the disease. In these cases, the disorder is described as idiopathic.¹⁶

The onset of aHUS ranges from before birth (prenatally) to adulthood. In young children, the disorder often develops suddenly and usually follows an infection, particularly an upper respiratory infection or gastroenteritis.¹³ Many affected individuals present with vague feelings of illness, fatigue, irritability, and lethargy that can potentially lead to hospitalization. The early phases may be difficult to diagnose, and the condition tends to be progressive.¹³ The vast majority of patients will have abnormal lactate dehydrogenase activity, acute kidney injury, haematuria (blood in urine), microangiopathic haemolytic anaemia, and proteinuria (high urine protein levels).¹⁵ An accurate differential diagnosis of aHUS requires ruling out other major types of thrombotic microangiopathy (TMA). Such as Shiga toxin-producing *Escherichia coli* (STEC)-HUS, thrombotic thrombocytopenic purpura (TTP), and disseminated intravascular coagulation (DIC).¹⁷

Patients are at constant risk of sudden and progressive damage, and failure of vital organs. One in 5 patients has aHUS affecting organs other than the kidneys, most commonly the brain or heart.¹⁸ Most patients with aHUS do not recover kidney function and need long term dialysis. Kidney transplants in these individuals unfortunately often fail because disease recurs in the new kidney.¹⁹

CLINICAL NEED AND BURDEN OF DISEASE

Onset of aHUS occurs in childhood more frequently than in adulthood (around 60% and 40% of all cases respectively). Most children (70%) who develop aHUS will experience the disease for the first time before the age of 2 years. The true incidence and prevalence of aHUS in England is uncertain because some patients remain undiagnosed.

Worldwide, the prevalence of aHUS ranges from 2.7–5.5 per million population, with an incidence of about 0.40 per million population.¹⁸ There are at present about 140 known patients in England, but there are probably many further patients in whom the diagnosis has been missed. In the area of England where it can be expected that all cases are fully ascertained (no missed diagnoses) the prevalence is 5.5 per million, which if applied to the whole of England implies a total of approximately 300 patients in England at present. This estimate is expected to rise over the coming years due to the use of the current treatment that has prolonged the life of aHUS patients.²⁰

Mortality rates range from 10 to 15% in the acute phase of the disease and, within a year of diagnosis, up to 70% of patients progress to end-stage renal failure and need dialysis or die.¹⁸

PATIENT TREATMENT PATHWAY

PATIENT PATHWAY

The care pathway for new patients will start with a suspected diagnosis of aHUS. Referring clinicians will contact the expert centre providing the service; the expert centre will confirm or reject the diagnosis using an agreed diagnostic checklist and appropriate laboratory testing. Patients with a confirmed diagnosis will be eligible for treatment with eculizumab in line with NHS England policy. The expert centre will confirm to the referring clinician that the patient is in scope for use of eculizumab, providing detailed care planning and will keep detailed records of all patients who are referred and accepted.

Patients will remain under the care of local clinicians using shared care protocols (except where the patient is local to the national service provider). The national service provider will provide ongoing clinical supervision of all patients with a confirmed diagnosis of aHUS, including those in whom eculizumab therapy is discontinued. The drug can be dispensed and given to patients anywhere in England, including at home.

These protocols will be set out in a written agreement between expert centre and user centres to ensure the requirements on both parties in the ongoing management of patients are clearly defined. The national service provider will also ensure where appropriate that the patient has been referred to a local medical genetics service or the genetics service at the national centre.²⁰

CURRENT TREATMENT OPTIONS

Eculizumab is an effective treatment for aHUS. NICE Highly specialised technologies guidance (HST1) recommends funding of eculizumab, within its marketing authorisation for the treatment of aHUS patients, only if all the following arrangements are in place:¹⁸

- coordination of eculizumab use through an expert centre
- monitoring systems to record the number of people with a diagnosis of atypical haemolytic uraemic syndrome and the number who have eculizumab, and the dose and duration of treatment
- a national protocol for starting and stopping eculizumab for clinical reasons
- a research programme with robust methods to evaluate when stopping treatment or dose adjustment might occur.

PLACE OF TECHNOLOGY

If licensed, ravulizumab will offer an additional first-line treatment option for patients with aHUS.

CLINICAL TRIAL INFORMATION

Trial	NCT02949128 , EudraCT 2016-002027-29, ALXN1210-aHUS-311; 12 years and older; ravulizumab; phase III
Sponsor	Alexion Pharmaceuticals
Status	Ongoing
Source of Information	Trial registry ⁴
Location	EU (incl UK), USA, Canada and other countries
Design	Single group assignment, open label
Participants	n=55 (planned); aged 12 years and older; males and females; thrombotic microangiopathy (TMA), including low platelet count, haemolysis, and decreased kidney function; documented meningococcal vaccination not more than 3 years prior to, or at the time of, initiating study drug.
Schedule	Participants will receive single loading dose of ravulizumab on day 1, followed by regular maintenance dosing beginning on day 15, based on weight. <ul style="list-style-type: none"> • ≥ 40 to <60 kg: 2400 mg loading, then 3000 mg every 8 weeks • ≥ 60 to <100 kg: 2700 mg loading, then 3300 mg every 8 weeks • ≥100 kg: 3000 mg loading, then 3600 mg every 8 weeks
Follow-up	Active treatment period: not specified Follow up period: 26 weeks
Primary Outcomes	Complete TMA response [Time Frame: 26 weeks]
Secondary Outcomes	Time Frame: 26 weeks <ul style="list-style-type: none"> • Dialysis requirement status • Time to Complete TMA Response • Complete TMA Response status over time • Observed value and change from baseline in estimated glomerular filtration rate (eGFR) • Change from baseline in chronic kidney disease (CKD) stage • Change from baseline in hematologic parameters (platelets, LDH, haemoglobin)

	<ul style="list-style-type: none"> • Increase in haemoglobin \geq 20g/L from baseline • Change from baseline in quality of life, as measured by the EQ-5D-3L (all patients) • Change from baseline in quality of life, as measured by the FACIT Fatigue Version 4 questionnaire (patients \geq 18 years of age) • Change from baseline in quality of life, as measured by the Paediatric FACIT Fatigue questionnaire (patients 12 to < 18 years of age)
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Study completion date reported as November 2020.

Trial	NCT03131219 , EudraCT 2016-002499-29, ALXN1210-aHUS-312; aged up to 18 years; ravulizumab; phase III
Sponsor	Alexion Pharmaceuticals
Status	Ongoing
Source of Information	Trial registry ²¹
Location	EU (incl UK), USA, Canada and other countries ^b
Design	Single group assignment, open label
Participants	n=16 (planned); aged up to 18 years; males and females; \geq 5 kg of weight at the time of consent; thrombotic microangiopathy (TMA), including low platelet count, haemolysis, and decreased kidney function; documented meningococcal vaccination not more than 3 years prior to dosing, and vaccination against <i>Streptococcus pneumoniae</i> and <i>Haemophilus influenzae</i> .
Schedule	Participants will receive single loading dose on day 1, followed by regular maintenance dosing beginning on day 15, based on weight.
Follow-up	Active treatment period: not specified. Follow up period: 26 weeks
Primary Outcomes	Complete TMA response [Time Frame: 26 weeks]
Secondary Outcomes	<p>Time Frame: 26 weeks</p> <p>Dialysis requirement status</p> <ul style="list-style-type: none"> • Time to Complete TMA response • Complete TMA Response status over time • Observed value and change from baseline in estimated glomerular filtration rate (eGFR) • Change from baseline in chronic kidney disease (CKD) stage • Change from baseline in hematologic parameters (platelets, lactate dehydrogenase (LDH), haemoglobin) • Increase in haemoglobin of \geq 20 g/L from baseline • Change from baseline in quality of life, as measured by Paediatric Functional Assessment of Chronic Therapy (FACIT) Fatigue questionnaire (patients \geq 5 years of age)
Key Results	-

^b Information provided by company

Adverse effects (AEs)	-
Expected reporting date	Study completion date reported as December 2020.

ESTIMATED COST

The cost of ravulizumab is not yet known.

The direct comparator of ravulizumab, eculizumab, costs £3,150 per 30 ml (10 mg/ml) vial (excluding VAT; British national formulary, online July 2018). The total cost of eculizumab per adult is estimated to be about £340,200 (initial and maintenance treatment) in the first year of treatment and about £327,600 for 1 year of treatment on the recommended maintenance dose.¹⁸

ADDITIONAL INFORMATION

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE Highly specialised technologies guidance. Eculizumab for treating atypical haemolytic uraemic syndrome (HST1). January 2015.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. Service Specification: Atypical haemolytic uraemic syndrome (aHUS) (all ages). 170008/S. April 2017.
- NHS England. Clinical Commissioning Policy: Eculizumab for atypical haemolytic uraemic syndrome. E03/PS(HSS)/a. September 2013.

OTHER GUIDANCE

- University Hospital of Wales: Children's Kidney Centre. Guidelines for the management and investigation of Haemolytic Uraemic Syndrome (HUS). June 2017.²²
- Clinical practice guidelines for the management of atypical haemolytic uraemic syndrome in the United Kingdom. 2010.²³

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