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HEALTH TECHNOLOGY BRIEFING
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Ravulizumab for treating generalised myasthenia gravis

NIHRIO ID	27159	**NICE ID**	10511
Developer/Company	Alexion Pharma UK	**UKPS ID**	660227

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

SUMMARY

Ravulizumab is currently in clinical development for the treatment of adults with generalised myasthenia gravis (gMG). gMG is a long-term autoimmune disorder where the body's own immune system mistakenly attacks healthy cells in the neuromuscular junction (NMJ). The NMJ is a region where nerve cells transmit signals to muscle cells to result in muscle contraction. The main symptom of gMG is weak muscles that tire easily, and this can negatively impact patient quality of life by making activities of daily living such as chewing, swallowing, talking and walking more challenging. Currently there are no medicinal products recommended by NICE specifically for the treatment of gMG, and medicines that are used can take a long time to work and result in side-affects.

Ravulizumab is a modified human antibody (a protein produced by the immune system) that is administered by intravenous (IV) infusion and works by blocking the protein C5. This protein is known to play a role in development of gMG by causing over-activation of the complement cascade (a pathway in the immune system) that results in the immune system attacking cells in the NMJ. Blocking the C5 protein results in improved communication between the nerve cells and muscle cells in the NMJ, and therefore improving the symptoms of gMG. If licensed, ravulizumab would be the first medicinal product approved by NICE for the treatment of gMG and reduce the treatment burden for these patients.

PROPOSED INDICATION

Treatment of adult patients with gMG.[1]

TECHNOLOGY

DESCRIPTION

Ravulizumab (Ultomiris, ALXN1210) is a monoclonal antibody $IgG_{2/4K}$ that specifically binds to the complement protein C5 in the terminal complement cascade.[1-3] A major driver of gMG is complement cascade activation.[4] The complement cascade is a part of the body's immune system which over-responds when activated in an uncontrolled manner, leading the body to attack its own healthy cells.[3] Ravulizumab specifically binding to C5 inhibits the cleavage of C5 to C5a (the initiating subunit of the terminal complement complex [C5b-9]) and prevents the generation of C5b-9. Ravulizumab preserves the early components of the complement activation that are essential for opsonisation of microorganisms and clearance of immune complexes.[2]

Ravulizumab is in clinical development for the treatment of adult patients with gMG. In the phase III trial (NCT039220293, Eudra CT 2018-003243-39), participants are given a concentrated sterile, preservative free-aqueous solution (10mg/ml) in single-use, 30mL vial for IV infusion. Single loading dose on day 1, followed by regular, weight-based maintenance dosing beginning on day 15, every 8 weeks, for 26 weeks.[1,5,6]

INNOVATION AND/OR ADVANTAGES

The National Institute for Health and Care Excellence (NICE) currently do not have specific guidance for treating gMG, ravulizumab would be the first medicinal product to receive Marketing Authorisation for this disease.[7] Current treatment approaches often involves the use of the drug pyridostigmine, steroids and immunosuppression medication. However, these treatments are associated with long term side-effects, often intolerable for patients and can take several months to become effective.[8,9]

Other medicinal products are in development for the treatment of gMG that also work by inhibiting complement protein C5. However, these treatments must be administered every 2 weeks resulting in a high treatment burden and reduced treatment adherence.[10] Ravulizumab has been designed in order to confer a long half-life of the antibody so that it is only necessary to administer to patients every 8 weeks.[8] In the pivotal phase III trial, patients that received ravulizumab demonstrated clinically meaningful improvements in their quantitative myasthenia gravis (QMG) score and myasthenia gravis – activities of daily living (MG-ADL) score. These improvements in scores were observed as early as week 1 and sustained throughout the 26 week trial period.[6]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Ravulizumab currently has Marketing Authorisation in the EU/UK for the following indications:[2]

- Treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH)
  - in patients with haemolysis with clinical symptoms indicative of high disease activity
  - in patients who are clinically stable after having been treated with eculizumab for at least the previous 6 months

- Treatment of patients with a body weight of 10kg 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.

Very common side effects of ravulizumab (affecting ≥ 1 in 10 people) include: upper respiratory tract infection, nasopharyngitis, headache, diarrhoea, nausea, pyrexia and fatigue.[2]

Ravulizumab is also currently in phase II/III clinical development for the treatment of: neuromyelitis optica; amyotrophic lateral sclerosis; thrombotic microangiopathy; COVID-19 (including severe viral pneumonia, acute lung injury and acute respiratory distress syndrome); acute kidney injury; lupus nephritis; and immunoglobulin A nephropathy.[11]

PATIENT GROUP

DISEASE BACKGROUND

Myasthenia gravis is chronic, autoimmune neuromuscular disorder primarily characterised by muscle weakness and excessive muscle fatigue.[12,13] Myasthenia gravis is an autoimmune condition whereby the immune system mistakenly produces antibodies that attack acetylcholine receptors (ACHRs) in the NMJ.[14] This impairs communication between the nerves and muscles, resulting in weak muscles that get easily tired.[13,15] The exact cause of myasthenia gravis is currently unknown although the disease has been linked to issues with the thymus gland which is often enlarged in people with myasthenia gravis and 1 in 10 people have an abnormal growth of the thymus (thymoma).[15] In most affected individuals the disease appears spontaneously with no family history of the disease, however there is an increased risk in individuals with a tendency to develop autoimmune condions.[12-14]

The condition can vary in severity and distribution of muscle weakness between individuals. Myasthenia gravis may be restricted to certain muscle groups or it may be more generalised (generalised myasthenia gravis), where multiple muscle groups are involved.[13]

People with gMG may experience the following symptoms that can make routine activities of daily living challenging: drooping of one of both eyelids (ptosis); blurred or double vision (diplopia); a change in facial expression; difficulty swallowing; shortness of breath; impaired speech (dysarthria); and weakness in the arms, hands, fingers, legs and neck.[16,17] Severity of the disease can also vary for each individual patient due to periods of relapse and periods of remission.[12] Muscle weakness in patients with myasthenia gravis worsens after periods of activity and improves after periods of rest.[16] Around 10% of patients may develop potentially life-threatening complications due to severe involvement of muscles used during breathing, which is known as a myasthenic crisis.[13]

CLINICAL NEED AND BURDEN OF DISEASE

Myasthenia gravis is a rare disease, affecting around 15 in every 100,000 people in the UK.[12] Although the disorder may become apparent at any age, symptom onset typically starts in adulthood; in women under 40 and men over 60.[13,15] Peak incidence rates occur in the third decade of life in women and sixth or seventh decade in men.[18]

In England (2019/20) there were 4,607 finished consultant episodes where myasthenia gravis (ICD-10 code G70.0) was recorded as the primary diagnosis which resulted in 3,537 admissions, 2,041 day cases and 16,060 FCE bed days.[19]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Treatments for gMG involve trying to keep the symptoms under control so the patient is able to live a largely normal life, these include: [20]

- medicines that help to reduce muscle weakness
- avoiding triggers (tiredness, stress, infections, certain medications which trigger symptoms)

In patients with an unusually large thyroid gland, surgery to remove the thymus gland (thymectomy) may sometimes be recommended.[20]

CURRENT TREATMENT OPTIONS

There are currently no treatment options approved by NICE for the treatment of gMG.[7]

Eculizumab has been approved by the EMA for the treatment of myasthenia gravis but has not been recommended by NICE.[21,22]

The following medicines are sometimes given to control symptoms of the disease:[20,23]

- pyridostigmine
- steroids (such as prednisolone)
- immunosuppressants (azathioprine and methotrexate).[23]

PLACE OF TECHNOLOGY

If licenced, ravulizumab would be the first medicinal product available in the UK, specifically approved patients with gMG, who currently have limited treatment options available.

CLINICAL TRIAL INFORMATION

Trial	NCT03920293; 2018-003243-39; A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Safety and Efficacy of Ravulizumab in Complement-Inhibitor-Naïve Adult Patients With Generalized Myasthenia Gravis

	Phase III – Active, not recruiting **Locations:** 9 EU countries, USA, Canada, and other countries **Estimated Primary Completion Date:** December 2021
Trial design	Randomised, double-blind, placebo-controlled, parallel-assignment
Population	N=175; adults aged 18 years and older; diagnosed with MG at least 6 months prior to screening; myasthenia gravis foundation of America clinical classification class II to IV at screening; myasthenia gravis-activities of daily living (MG-ADL) profile must be ≥6 at screening and randomization
Intervention(s)	Ravulizumab 10mg/ml in single-use 30ml vial (intravenous infusion)
Comparator(s)	Placebo (IV infusion)
Outcome(s)	Primary outcome measure: • Change from baseline in MG-ADL See trial record for full list of outcome measures
Results (efficacy)	The study met, with high statistical significance, the primary endpoint MG-ADL total score, a patient-reported assessment at week 26, and for the subset of patients who have completed 26 weeks in the extension study to date, the positive treatment effect was maintained through a total of 52 weeks.[24]
Results (safety)	Ravulizumab was well tolerated with a safety profile consistent with that observed in phase 3 studies in PNH and aHUS.[24]

ESTIMATED COST

The estimated cost of ravulizumab is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

No relevant guidance identified.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2014/15 NHS Standard Contract for Neuromuscular Operational Delivery Network Specification. D04/ODN/a.
- NHS England. 2013/14 NHS Standard Contract for Neurosciences: Specialised Neurology (Adult). D04/S/a.

OTHER GUIDANCE

- American Academy of Neurology. International Consensus Guidance for Management of Myasthenia Gravis. 2020. [25]
- Association of British Neurologists. Myasthenia gravis management guidelines. 2018.[9]

ADDITIONAL INFORMATION

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