NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Ravulizumab for treating refractory antibody positive generalised myasthenia gravis

Draft scope

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of ravulizumab within its marketing authorisation for treating refractory antibody positive generalised myasthenia gravis.

Background

Myasthenia gravis is a long-term condition which causes certain muscles to become weak and tire easily. It is caused by a problem with the immune system, which mistakenly produces antibodies against the nicotinic acetylcholine receptor (AChR) or muscle-specific tyrosine kinase (MuSK). The antibodies block the chemical signals between nerves and muscles, meaning that muscles are unable to tighten (contract). The thymus gland is the main source of the abnormal antibodies. The muscles around the eyes are commonly affected first, which causes drooping of the eyelid and double vision. Muscles controlling facial expression, chewing, swallowing, speaking and, less commonly, breathing and neck and limb movements can also be affected. When muscle groups other than the eye muscles are affected, the condition is known as generalised myasthenia gravis. In very severe cases, muscle weakness causes life-threatening difficulties with breathing and swallowing. This is known as myasthenic crisis.

Myasthenia gravis affects about 15 in every 100,000 people in the UK.[1] It can develop at any age, but most commonly affects women under 40 years of age and men over 60 years of age.[2,3] About 80% to 90% of people with myasthenia gravis have detectable antibodies against AChR, while 3% to 7% have antibodies against MuSK.[4-6] It is difficult to estimate the number of people with myasthenia gravis whose disease does not respond to currently available treatments; estimates range from about 10% to 20%.[7,8]

Mild myasthenia gravis and some cases of moderate disease are usually treated with cholinesterase inhibitors such as pyridostigmine which delay the breakdown of acetylcholine, the chemical which stimulates muscle contraction.[9] If treatment with cholinesterase inhibitors is not effective, or they are not suitable for long term use, then corticosteroid tablets such as prednisolone are used. Immunosuppressive therapies such as azathioprine are offered in addition to steroids, with the aim of reducing the steroid dose over time. If the disease does not respond to the first immunosuppressive treatment, alternative immunosuppressants may be offered (including mycophenolate mofetil, methotrexate, ciclosporin and rituximab). Surgery to remove the thymus gland (thymectomy) is an option for people with mild disease and antibodies against AChR, and people with moderate or severe disease. Myasthenic crisis is treated in hospital with mechanical ventilation, intravenous injections of antibodies (immunoglobulins) from healthy donor blood, or by removing plasma from the blood to reduce the number of abnormal antibodies (known as plasmapheresis or plasma exchange) and supportive care.[9]

The technology

Ravulizumab (Ultomiris, Alexion Pharma) is a modified human antibody (a protein produced by the immune system) which supresses immune responses by inhibiting part of the complement cascade. It is administered intravenously.

Ravulizumab does not currently have a marketing authorisation in the UK for treating generalised myasthenia gravis. It has been studied in a clinical trial, as monotherapy, compared with placebo in adults with generalised myasthenia gravis.

Intervention	Ravulizumab
Population	Adults with refractory generalised myasthenia gravis

Comparators	Established clinical management without ravulizumab including:
	• Immunosuppressants
	  ○ Eculizumab
	  ○ Rituximab (does not currently have a marketing authorisation in the UK for this indication)
	• Intravenous immunoglobulin
	• Plasma exchange
	• Thymectomy
	• Best supportive care (including includes deep venous thrombosis prophylaxis; ulcer prophylaxis; adequate nutrition and hydration; and avoidance of infections and drugs that may worsen myasthenia symptoms)

Outcomes	The outcome measures to be considered include: • mortality • number of hospitalisations • adverse effects of treatment • health-related quality of life.

Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability of any managed access arrangement for the intervention will be taken into account.
Other considerations	If the evidence allows the following subgroups will be considered. These include: • disease severity (mild, moderate, severe) • classification (class II, III, IV or V) • treatment history (untreated or treatment refractory disease) • number of previous treatments (1, 2 or more previous treatments) The availability and cost of biosimilar and generic products should be taken into account. Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations	**Terminated appraisals:** Eculizumab for treating refractory myasthenia gravis (terminated appraisal) (2020). NICE Technology Appraisal 636. **Related Guidelines:** Suspected neurological conditions: recognition and referral (2019). NICE guideline 127. Review date: TBC **Related Quality Standards:** Suspected neurological conditions: recognition and referral (2021). NICE quality standard 198
Related National Policy	The NHS Long Term Plan, 2019. NHS Long Term Plan

	NHS England (2018) Clinical Commissioning Policy: Rituximab bio-similar for the treatment of myasthenia gravis (adults). 170084P. 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 NHS England (2018) Updated Commissioning Guidance for the use of therapeutic immunoglobulin (Ig) in immunology, haematology, neurology and infectious diseases in England NHS England (2021) Highly specialised services 2019 Diagnostic service for rare neuromuscular disorders (adults and children) p.38 NHS England (2018/2019) NHS manual for prescribed specialist services (2018/2019). Chapter 11: Adult specialist neurosciences services, Chapter 12: Adult specialist ophthalmology services Chapter 48: Diagnostic service for rare neuromuscular disorders (adults and children) Department of Health and Social Care, NHS Outcomes Framework 2016-2017: Domains 1 and 2. https://www.gov.uk/government/publications/nhs-outcomes-framework-2016-to-2017

Questions for consultation

Is the Myasthenia Gravis Foundation of America (MGFA) classification system used in the NHS? Would ravulizumab be used in people with myasthenic crisis (MGFA class 5)?

How is refractory generalised myasthenia gravis determined or defined clinically?

Have all relevant comparators for ravulizumab been included in the scope?

Which treatments are considered to be established clinical practice in the NHS for refractory generalised myasthenia gravis? Is eculizumab a relevant comparator?

How should best supportive care be defined?

Are the outcomes listed appropriate?

Are the subgroups suggested in 'other considerations' appropriate? Are there any other subgroups of people in whom ravulizumab is expected to be more clinically effective and cost effective or other groups that should be examined separately?

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected

characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which ravulizumab will be licensed;

- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;

- could have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

Do you consider ravulizumab to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?

Do you consider that the use of ravulizumab can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?

Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.

To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.

NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/article/pmg19/chapter/1-Introduction).

References

1 Spillane J, Higham E, Kullmann DM (2012) Myasthenia gravis. *BMJ*; 345:e8497.

2 Patient (2017) Myasthenia Gravis. Accessed February 2022.

3 Meriggioli MN and Sanders DB (2009) Autoimmune myasthenia gravis: emerging clinical and biological heterogeneity. *Lancet Neurology*; 8(5):475-90.

4 Guptill JT and Sanders DB (2010) Update on muscle-specific tyrosine kinase antibody positive myasthenia gravis. *Current Opinion Neurology*; 23(5):530-5.

5 Ruff RL and Lisak RP (2018) Nature and action of antibodies in myasthenia gravis. *Neurologic Clinics*; 36(2):275-91.

6 Maddison P, Ambrose PA, Sadalage G et al. (2019) A Prospective Study of the Incidence of Myasthenia Gravis in the East Midlands of England. *Neuroepidemiology*; 53(1-2):93-99.

7 Mantegazza R and Antozzi C (2018) When myasthenia gravis is deemed refractory: clinical signposts and treatment strategies. *Therapeutic Advances in Neurological Disorders*; 11:1756285617749134.

8 Schneider-Gold C, Hagenacker T, Melzer N et al. Understanding the burden of refractory myasthenia gravis. *Therapeutic Advances in Neurological Disorders*; 12:1756286419832242.

9 BMJ Best Practice (2021) Myasthenia gravis. Accessed February 2022.