Eculizumab and Efgartigimod for the Treatment of Myasthenia Gravis

Draft Background and Scope

March 15, 2021

Background

Myasthenia Gravis (MG) is an autoimmune disease that affects the neuromuscular junction. The prevalence in the United States is estimated to be between 14 and 20 per 100,000 people[1,2] and the annual incidence is approximately 2.2 per 100,000.[3]

The characteristic finding of MG is progressive weakening of a muscle with repeated use.[4] It typically starts with facial muscles (drooping eyelids with repeated blinking) but can progress to affect the entire body (generalized disease); when the diaphragm is involved, this can result in life-threatening respiratory failure requiring intubation.[5] The majority of patients (~80%) progress to some form of generalized disease.[3,5]

In the classic form, patients have autoantibodies to the acetylcholine receptor.[4] First-line treatment is pyridostigmine, which inhibits the breakdown of acetylcholine.[6] With progressive disease, high-dose corticosteroids are used to rapidly control symptoms, followed by conventional immunosuppressive drugs (azathioprine, mycophenolate mofetil) in order to reduce the corticosteroid dose while maximizing patients' quality of life. The goal of therapy is to maintain the patient with minimal manifestations of disease or better with minimal side effects.[6] Approximately 20,000 patients with generalized MG are intolerant or have inadequate response to conventional treatment options.[7] The average annual cost per patient for MG-specific care paid by a private health plan was $15,675 in 2009.[8] The largest costs were home health services and intravenous immunoglobulin (IVIG) infusions.

New therapies are becoming available for patients with MG. Eculizumab is a monoclonal antibody that inhibits the cleavage of C5, which reduces complement activation.[9] It received FDA approval in October 2017 for the treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AchR) antibody positive.[10] Efgartigimod is an antibody fragment that targets the neonatal Fc receptor and reduces IgG antibody levels by about 50%.[11] An FDA decision on efgartigimod is expected on December 17, 2021.[12]

Stakeholder Input

This Draft Scoping Document was developed with input from diverse stakeholders, including patient advocacy organizations, clinicians, researchers, and manufacturers of the agents of focus in this review. This document incorporates feedback gathered during preliminary calls with stakeholders and open input submissions from the public. A Revised Scoping Document will be posted following a three-week public comment period. ICER looks forward to continued engagement with stakeholders throughout its review and encourages comments to refine our understanding of the clinical effectiveness and value of treatments for MG.

Patients often experience a long and frustrating path to diagnosis and appropriate treatment. This reflects the paucity of experience physicians have in caring for patients with MG because the disease is rare. Patients are misdiagnosed and bounce around between many specialists before they receive the diagnosis of MG. Patients also experience significant side effects from current therapies, such as corticosteroids. The side effects can contribute as much to patient disability as the disease itself. Patient advocates feel that the manufacturers downplay the impact of side effects on patients' lives. In addition, patients experience significant barriers accessing some therapies. They particularly highlighted the use of IVIG as maintenance therapy. Patients also highlighted the importance of the caregiver role and the impact of MG on their lives.

Stakeholders highlighted that eculizumab is very expensive. They also noted that the Phase 3 pivotal trial of eculizumab studied patients with refractory disease, but that the FDA label was broader. This has led to widespread use of the drug in patients who have not received an adequate trial of conventional immunosuppressive therapy, which is much less expensive.

Report Aim

This project will evaluate the health and economic outcomes of both eculizumab and efgartigimod for myasthenia gravis. The ICER value framework includes both quantitative and qualitative comparisons across treatments to ensure that the full range of benefits and harms – including those not typically captured in the clinical evidence such as innovation, public health effects, reduction in disparities, and unmet medical needs – are considered in the judgments about the clinical and economic value of the interventions.

Scope of Clinical Evidence Review

The proposed scope for this assessment is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence will be abstracted from randomized controlled trials as well as high-quality systematic reviews; high-quality comparative cohort studies will be considered, particularly for long-term outcomes and

uncommon adverse events. Our evidence review will include input from patients and patient advocacy organizations, data from regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see ICER's grey literature policy).

All relevant evidence will be synthesized qualitatively or quantitatively. Wherever possible, we will seek out head-to-head studies of the interventions and comparators of interest. Data permitting, we will also consider combined use of direct and indirect evidence in network meta-analyses of selected outcomes. Full details regarding the literature search, screening strategy, data extraction, and evidence synthesis will be provided after the revised scope in a research protocol published on the Open Science Framework website (https://osf.io/7awvd/).

Population

The population of focus for the review is adults with generalized myasthenia gravis, defined by Myasthenia Gravis Foundation of America (MGFA) clinical classes of II to IV for whom conventional immunosuppressive therapies have not been effective or have not been tolerated.

As data permit, we will evaluate the evidence on the following subpopulations:

- Patients with anti-acetylcholine receptor antibodies
- Patients without anti-acetylcholine receptor antibodies

Interventions

The two interventions of interest for this review are:

- Eculizumab (Soliris®, Alexion Pharmaceuticals, Inc.)
- Efgartigimod (argenx)

Both are added to conventional therapy (thymectomy when appropriate, acetylcholinesterase inhibitor, corticosteroids and/or non-steroidal immunosuppressive therapy) for maintenance therapy in patients with generalized MG.

Comparators

Data permitting, we intend to compare the agents to each other and to the following:

- Conventional therapy
- Maintenance IVIG therapy

Outcomes

The outcomes of interest are described in the list below.

- Patient-Important Outcomes
    - Minimal symptoms or better
    - Quality of life (MG Quality of Life, 15, revised; Myasthenia Gravis Activities of Daily Living; EQ-5D; etc.)
    - Fatigue (Neurology Quality of Life, etc.)
    - Hospitalizations
    - Myasthenia crisis
    - Return to work
    - Corticosteroid side effects (diabetes, osteoporosis, cataracts, infections, psychological, etc.)
    - Corticosteroid dose ≤ 5 mg prednisone equivalents
    - Adverse events including:
        - Serious adverse events
        - Adverse events leading to drug discontinuation
        - Infections
        - Malignancies
        - Death
- Other Outcomes
    - Manual Muscle Test (MMT)
    - MG Composite Score (MGC)
    - MGFA Post-Intervention Status (MGFA-PIS)
        - Complete Stable Remission (CSR)
        - Pharmacologic Remission (PR)
        - Minimal Manifestations (MM)
    - Quantified MG (QMG)

Timing

Evidence on intervention effectiveness and harms will be derived from studies of at least four weeks duration.

Settings

All relevant settings will be considered, with a focus on patients treated in outpatient settings in the United States.

Potential Other Benefits and Contextual Considerations

Our reviews seek to provide information on potential other benefits offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. These general elements (i.e., not specific to a given disease) are listed in the table below.

Table 1.2. Categories of Contextual Considerations and Potential Other Benefits or Disadvantages

Contextual Consideration
Acuity of need for treatment of individual patients based on the severity of the condition being treated
Magnitude of the lifetime impact on individual patients of the condition being treated
Other (as relevant)

Potential Other Benefit or Disadvantage
Patients' ability to achieve major life goals related to education, work, or family life
Caregivers' quality of life and/or ability to achieve major life goals related to education, work, or family life
Patients' ability to manage and sustain treatment given the complexity of regimen
Health inequities
Other (as relevant)

ICER encourages stakeholders to provide input on these elements in their public comment submissions.

Scope of Comparative Value Analyses

As a complement to the evidence review, we will develop an economic model to assess the lifetime cost effectiveness of eculizumab and efgartigimod, in addition to conventional therapy (i.e., acetylcholinesterase inhibitor, corticosteroids and/or non-steroidal immunosuppressive therapy), compared with conventional therapy alone. We will not be comparing eculizumab and efgartigimod to conventional therapy plus IVIG as it is unlikely that IVIG would be widely adopted due to limitations in its supply. The model structure will be based in part on a literature review of prior published models of MG, with a focus on patients with MGFA classes II to IV. The base-case analysis will take a health care system perspective (i.e., focus on direct medical care costs only). Data permitting, productivity impacts and other indirect costs will be considered in a separate analysis from a modified societal perspective. This modified societal perspective analysis will be considered as a co-base case when the societal costs of care are large relative to direct health care costs, and the impact of treatment on these costs is substantial. This will most often occur in cases where the incremental cost-effectiveness ratio changes by greater than 20%, greater than $200,000 per QALY, and/or when the result crosses the threshold of $100,000-$150,000 per QALY gained.

The target population will consist of adults with generalized myasthenia gravis, defined by MGFA clinical classes inclusive of II through IV, for whom conventional immunosuppressive therapies have not been effective or have not been tolerated. Given available data, the model will consist of health states including 1) symptomatic MG (multiple states based on quality of life); 2) remission or minimal manifestation; 3) myasthenic crisis; 4) death. The collapsing of health states may be considered if treatment effects are not reported across all living health states. The model will also incorporate separate states for symptomatic patients with differing levels of quality of life, depending on symptom scales. Treatment-related adverse events leading to measurable disutility will also be considered for inclusion in the model. A cohort of patients will transition between states during predetermined three-month cycles, over a lifetime time horizon, modeling patients from treatment initiation until death. In addition, cost effectiveness will be estimated for shorter time horizons (e.g., five years). Since eculizumab is indicated only in the subgroup of patients with anti-acetylcholine receptor antibodies, the analysis involving eculizumab will be conducted in this subgroup only.

Key model inputs will include clinical probabilities, quality-of-life values, and health care costs. Probabilities, costs, and other inputs will differ to reflect varying effectiveness among interventions. Treatment effectiveness will be estimated using network meta-analysis or meta-analysis if sufficient data exist. If meta-analysis is not feasible, the results from the pivotal clinical trials will be used as the estimate of treatment effectiveness.

Health outcomes and costs will be dependent on time spent in each health state, clinical events, adverse events (AEs), and direct medical costs. The health outcome of each intervention will be evaluated in terms of time in remission/minimal manifestation (in years), life-years gained (LYG), quality-adjusted life years (QALYs) gained, and equal value of life years gained (evLYG). Additional clinical and patient status or quality-of-life outcome measures may be considered for inclusion in the model analysis plan. Quality-of-life (utility) weights will be applied to each health state, including quality-of-life decrements for serious adverse events. The model will include direct medical costs, including but not limited to costs related to drug administration, drug monitoring, condition-related care, and serious adverse events. In addition, productivity changes and other indirect costs will be included in a separate analysis if available data allow. Relevant pairwise comparisons will be made between treatments, and results will be expressed in terms of the marginal cost per QALY gained, cost per evLYG, cost per life-year gained, cost per time in remission/minimal manifestation, and cost per remission/minimal manifestation gained. Additional cost-consequence measures will be evaluated for inclusion in the model analysis plan.

In separate analyses, we will explore the potential health care system budgetary impact of treatment over a five-year time horizon, utilizing published or otherwise publicly available information on the potential population eligible for treatment and results from the economic model for treatment costs and cost offsets. This budgetary impact analysis will indicate the relation

between treatment prices and level of use for a given potential budget impact and will allow assessment of any need for managing the cost of such interventions. More information on ICER's methods for estimating potential budget impact can be found here.

Identification of Low-Value Services

ICER includes in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create additional resources in health care budgets for higher-value innovative services (for more information, see ICER's Value Assessment Framework). These services are not ones that would be directly affected by eculizumab or efgartigimod (e.g., use of azathioprine), as these services will be captured in the economic model. Rather, we are seeking services used in the current management of myasthenia gravis beyond the potential offsets that arise from a new intervention. ICER encourages all stakeholders to suggest services (including treatments and mechanisms of care) that could be reduced, eliminated, or made more efficient. We have reviewed the Choosing Wisely recommendations of the Neurology professional societies and none of them seem to apply.

References

1. Carr AS, Cardwell CR, McCarron PO, McConville J. A systematic review of population based epidemiological studies in Myasthenia Gravis. *BMC Neurol.* 2010;10:46.
2. Howard Jr J. Myasthenia Gravis Clinical Overview. https://myasthenia.org/Professionals/Clinical-Overview-of-MG. Published 2015. Accessed.
3. Hendricks TM, Bhatti MT, Hodge DO, Chen JJ. Incidence, Epidemiology, and Transformation of Ocular Myasthenia Gravis: A Population-Based Study. *Am J Ophthalmol.* 2019;205:99-105.
4. Gilhus NE. Myasthenia Gravis. *N Engl J Med.* 2016;375(26):2570-2581.
5. Grob D, Brunner N, Namba T, Pagala M. Lifetime course of myasthenia gravis. *Muscle Nerve.* 2008;37(2):141-149.
6. Sanders DB, Wolfe GI, Benatar M, et al. International consensus guidance for management of myasthenia gravis: Executive summary. *Neurology.* 2016;87(4):419-425.
7. Phillips G. argenx Public Comment Submission. In:2021.
8. Guptill JT, Sharma BK, Marano A, Soucy A, Krueger A, Sanders DB. Estimated cost of treating myasthenia gravis in an insured U.S. population. *Muscle Nerve.* 2012;45(3):363-366.
9. Kaplan M. Eculizumab (Alexion). *Curr Opin Investig Drugs.* 2002;3(7):1017-1023.
10. FDA. SOLIRIS® (eculizumab) injection, for intravenous use. In: Administration FaD, ed. Food and Drug Administration2017.
11. Ulrichts P, Guglietta A, Dreier T, et al. Neonatal Fc receptor antagonist efgartigimod safely and sustainably reduces IgGs in humans. *J Clin Invest.* 2018;128(10):4372-4386.
12. argenx Announces FDA Acceptance of BLA Filing for Efgartigimod for the Treatment of Generalized Myasthenia Gravis [press release]. March 2, 2021 2021.