Eculizumab and Efgartigimod for the Treatment of Myasthenia Gravis: Final Policy Recommendations

October 20, 2021

Policy Recommendations

Introduction

The following policy recommendations reflect the main themes and points made during the Policy Roundtable discussion at the September 24th New England CEPAC public meeting on the use of eculizumab and efgartigimod for the treatment of myasthenia gravis. At the meeting, ICER presented the findings of its revised report on these treatments and the New England CEPAC voting council deliberated on key questions related to their comparative clinical effectiveness, potential other benefits and contextual considerations, and long-term value for money at current prices. Following the votes, ICER convened a Policy Roundtable of two patients, two clinical experts, two payers, and one representative from a pharmaceutical manufacturer to discuss how best to apply the evidence and votes to real-world practice and policy. The discussion reflected multiple perspectives and opinions, and therefore, none of the statements below should be taken as a consensus view held by all participants.

A recording of the conversation can be accessed here and a recording of the voting portion of the meeting can be accessed here. More information on Policy Roundtable participants, including conflict of interest disclosures, can be found in the appendix of this document. ICER's report on these treatments, which includes the same policy recommendations, can be found here.

The roundtable discussion was facilitated by Dr. Steven Pearson, MD, MSc, President of ICER. The main themes and recommendations from the discussion are organized by audience and summarized below.

All Stakeholders

All stakeholders have a responsibility and an important role to play in ensuring that effective new treatment options for patients with generalized myasthenia gravis are introduced in a way that will help reduce health inequities.

Safe and effective treatment for gMG remains a significant unmet health care need. Efforts are needed to ensure that new therapies for myasthenia gravis such as eculizumab and efgartigimod, improve the health of patients and families and do not aggravate existing health inequities. Clinical experts and patients highlighted that the high cost of new therapies may worsen disparities in accessing care. This may be due to lack of health insurance that limits access to specialists and the new therapies that they prescribe, or high deductible payments even for those with insurance may result in steep out of pocket costs. The cost of care is not the only factor that may contribute to health inequities. Patient representatives at the meeting noted that Black and African American women are diagnosed at earlier ages and carry a particularly high lifetime burden of disease, but

this population is particularly vulnerable to access challenges both to neuromuscular specialist care and to expensive new therapies.

To address these concerns:

Manufacturers should take the following actions:

- Set the price for new treatments for gMG in alignment with added benefits for patients.
- Take steps necessary to include a more diverse patient population in clinical trials, including an adequate number of patients with diverse ages, genders, and ethnic and racial backgrounds.

Payers should take the following actions:

- Ensure that benefit designs developed in conjunction with employers and other plan sponsors do not create requirements for out-of-pocket spending that create major barriers to appropriate access for vulnerable patients when the price is in alignment with the clinical benefits for patients

Clinical specialty societies should take the following actions:

- Develop and disseminate educational materials and create measurable goals to demonstrate that clinicians are aware of the challenges of diagnosing gMG with particular attention given to providers caring for diverse patient populations
- Share learned protocols for medical treatments which have been successful, and unsuccessful, for treatment of diverse patient populations

Payers

Payers should use the FDA label as the guide to coverage policy and engage clinical experts and diverse patient representatives in considering how to address coverage issues for which there is limited or no evidence at the current time.

Given the significant uncertainty that remains about the new therapies for gMG, it is reasonable for payers to use prior authorization as a component of coverage. Prior authorization criteria should be based on the FDA label, clinical trial eligibility criteria, specialty society guidelines, and input from clinical experts and patient groups. The process for authorization should be clear and efficient for providers and patients. General Fair Access Design Criteria set out in ICER's previous work are shown below, with perspectives on specific elements of coverage criteria for new therapies for gMG provided in the section on drug-specific considerations.

Cost Sharing

- Patient cost sharing should be based on the net price to the plan sponsor, not the unnegotiated list price.

- If all drugs in a drug class are priced so that they represent a fair value, it remains reasonable for payers to use preferential formulary placement with tiered cost sharing to help achieve lower overall costs.

Coverage Criteria: General

- Payers should offer alternatives to prior authorization protocols such as programs that give feedback on prescribing patterns to clinicians or exempt them from prior authorization requirements ("gold carding") if they demonstrate high fidelity to evidence-based prescribing.

- Payers should document at least once annually that clinical eligibility criteria are based on high quality, up-to-date evidence, with input from clinicians with experience in the same or similar clinical specialty.

- Clinical eligibility criteria should be developed with explicit mechanisms that require payer staff to document using an open and transparent process that is readily accessible to the public that they have:

    a. Considered limitations of evidence due to systemic under-representation of minority populations; and

    b. Sought input from clinical experts on whether there are distinctive benefits and harms of treatment that may arise for biological, cultural, or social reasons across different communities; and

    c. Confirmed that clinical eligibility criteria have not gone beyond reasonable use of clinical trial inclusion/exclusion criteria to interpret or narrow the FDA label language in a way that disadvantages patients with underlying disabilities unrelated to the condition being treated.

- If an initial request for coverage is denied, access to a peer-to-peer call should be rapid. Management of gMG is urgent. In many clinicians' experience, access to peer-to-peer calls is onerous and prolonged. Peer to peer calls facilitate the communication of individual patients' unique clinical characteristics and need for therapy. The physician peer should be knowledgeable and experienced in the management of gMG.

Drug-Specific Considerations

The lack of standardization of treatment protocols, substantial uncertainty about which patients will benefit most from which treatments, and high annual prices for newer treatments for gMG will all lead payers to develop prior authorization criteria and to consider other limits on utilization.

None of these limits, however, should undermine the tenets of fair access to which all patients have a fundamental right.[1] To explore the appropriate application of evidence to coverage policy, and to reflect the views of patient experts and clinicians on specific ways that payers might appropriately use coverage policy to manage resources prudently, we present the following perspectives on specific elements of cost sharing and coverage criteria for eculizumab and efgartigimod.

Coverage Criteria: Eculizumab

- **Diagnosis:** Payers have taken different approaches to diagnostic criteria. Some simply indicate that coverage is provided for gMG. Others specify that coverage is provided for gMG that is not limited to ocular only symptoms and persistent. And some payers include a requirement for one of the following, although clinical experts advised that these criteria are not highly specific for gMG:
    - History of abnormal neuromuscular transmission test demonstrated by single-fiber electromyography (SFEMG) or repetitive nerve stimulation
    - History of positive anticholinesterase test, e.g., a Tensilon/edrophonium chloride test (NB: as of 2018 FDA rescinded approval for edrophonium in the US due to high levels of false positive results and the growing use of AChR antibody testing as the new gold standard)
    - Patient has demonstrated improvement in MG signs on oral cholinesterase inhibitors, as assessed by the treating neurologist
- **Age:** Age criteria in payer coverage policies follow the FDA label, which is for adults ages 18 years and older. However, gMG can present at earlier ages and coverage may be appropriate in select cases. Payers should have efficient mechanisms, such as peer to peer communication with someone knowledgeable in treatments for gMG, to allow clinicians to seek coverage exceptions for patients with serious unmet need who are below the cutoff for the age necessary for coverage.
- **Clinical eligibility**: Coverage criteria across all insurers follow the FDA label and limit coverage to patients with gMG who test positive for antibodies to the AChR. Since the price of eculizumab far exceeds reasonable willingness to pay thresholds, it is reasonable for payers to focus coverage by using clinical trial eligibility criteria that are narrower than the

FDA label language. In particular, eculizumab was tested in what is considered "refractory" gMG, and most payers will therefore apply the following trial eligibility criteria as part of insurance criteria:

  - MGFA clinical classification class II to IV at initiation of therapy
  - MG-ADL total score ≥ 6 at initiation of therapy

  and

  - Failure of treatment with at least two immunosuppressive agents OR failed treatment with at least one immunosuppressive agent and the patient has required chronic plasma exchange of IVIG.

- **Exclusion criteria**: Patients must receive vaccination for meningococcus prior to starting therapy. Although history of thymoma or other neoplasms of the thymus and a history of thymectomy within 12 months of treatment initiation were exclusion criteria in clinical trials, clinical experts advising ICER suggested that there are circumstances in clinical practice in which the use of eculizumab would be appropriate for such patients.

- **Duration of coverage and renewal criteria**: There are no data to guide decisions on if or when to taper patients to lower doses of eculizumab. Clinical experts advised that it would be reasonable to require attestation of patient benefit (≥ 2 point improvement in the MG-ADL) for continuation of coverage.

- **Provider restrictions**: Clinical experts agreed that it is reasonable to restrict prescriptions for neurologists with expertise in the treatment of gMG (neuromuscular specialists). Given the limited supply of these specialists, allowing telehealth consultation for approval of prescribing by generalists would help to avoid disparities, particularly in rural areas with few specialists. Specialty clinicians are better suited to identify patients who are most likely to benefit, provide sufficient information for patients to make a well-informed decision, and monitor for response and side effects.

Coverage Criteria: Efgartigimod

- **Diagnosis:** Payers have taken different approaches in the past to diagnostic criteria in coverage policy for eculizumab for gMG. Some payers simply indicate that coverage is provided for gMG. Others specify that coverage is provided for gMG that is not limited to ocular involvement and persistent. And some payers include a requirement for one of the following, although clinical experts advised that these criteria are not highly specific for gMG:

- History of abnormal neuromuscular transmission test demonstrated by single-fiber electromyography (SFEMG) or repetitive nerve stimulation
- History of positive anticholinesterase test, e.g., a Tensilon/edrophonium chloride test (NB: FDA rescinded approval for edrophonium in the US due to high levels of false positive results and the growing use of AChR antibody testing as the new gold standard)
- Patient has demonstrated improvement in MG signs on oral cholinesterase inhibitors, as assessed by the treating neurologist

- **Age:** Age criteria are likely to follow the inclusion criteria for the pivotal trial, which will likely be for adults ages 18 years and older. However, gMG can present at earlier ages and coverage may be appropriate in select cases. Payers should have efficient mechanisms, such as peer to peer communication with someone knowledgeable in treatments for gMG, so that clinicians can seek coverage exceptions for patients with serious unmet need who are near the cutoff for the age necessary for coverage.

- **Clinical eligibility**: Prior to the FDA regulatory decision on efgartigimod it is not known whether the label will include all patients with gMG or whether it will be limited to patients with positive AChR antibodies. Coverage for treatment of antibody-negative patients would create a difficult choice for payers given that clinical trial data provided by the company on this relatively small subpopulation are "exploratory" and did not provide evidence of clinically significant benefits. Clinical experts advised that given the undoubted efficacy of plasmapheresis in patients with AChR negative gMG, and considering that efgartigimod has a functionally similar mechanism of action, that efgartigimod would be an appropriate therapy for select patients who have failed other therapies. Pending further data, payers deciding to limit coverage to the AChR-positive population should therefore ensure rapid consideration of exceptions through peer-to-peer conversation.

  Since the expected price of efgartigimod far exceeds a reasonable cost-effectiveness range, it is not unreasonable for payers to focus coverage by using clinical trial eligibility criteria that are narrower than the FDA label language. Most payers will therefore apply the following trial eligibility criteria as part of insurance criteria:

  - MGFA clinical classification class II to IV at initiation of therapy
  - MG-ADL total score ≥ 5, with ≥ 50% of the total score due to non-ocular symptoms at initiation of therapy

  and

- Receiving a stable dose ≥ 1 of the following: acetylcholinesterase inhibitors, steroids (at least 3 months of treatment), or at least 6 months of treatment with non-steroidal immunosuppressive therapy (NSIST).

Of note, the efgartigimod trial eligibility criteria were broader than that of eculizumab, and patients were not required to be "refractory" to IVIG and/or immunosuppressive therapies. This distinction may expand requests for use of efgartigimod over eculizumab and may lead payers to consider step therapy with less expensive agents (see section on step therapy below).

- **Exclusion criteria**: Although clinical trial exclusion criteria include history of thymectomy within 3 months, clinical experts advising ICER suggested that there are circumstances in clinical practice in which the use of efgartigimod would be appropriate for such patients.

- **Dosing criteria**: Some payers may wish to explore negotiating formal payment mechanisms that cap reimbursements to manufacturers. The goal would be to allow clinicians greater flexibility in dosing of efgartigimod to match patient clinical response while providing payers with a mechanism to manage total costs.

- **Duration of coverage and renewal criteria**: There are no data to guide decisions on if or when to taper patients to lower doses of efgartigimod. Clinical experts advised that it would be reasonable to require attestation of patient benefit (≥ 2-point improvement in the MG-ADL) for continuation of coverage.

- **Provider restrictions**: Clinical experts agreed that it is reasonable to restrict prescriptions for neurologists with expertise in the treatment of gMG (neuromuscular specialists). Given the limited supply of these specialists, allowing telehealth consultation for approval of prescribing by generalists would help to avoid disparities, particularly in rural areas with few specialists. Specialty clinicians are better suited to identify patients who are most likely to benefit, provide sufficient information for patients to make a well-informed decision, and monitor for response and side effects.

Step Therapy

Payers should use step therapy based on clinical trial eligibility and/or authoritative evidence-based clinical specialty guidelines as they become available. Given the limited current evidence base for efgartigimod, payers should not require therapy with efgartigimod prior to coverage of eculizumab. However, as additional clinical evidence accumulates, it may be reasonable to require step therapy based on price.

Given the limited evidence and cost, it is likely that health plans may choose to continue step therapy for eculizumab, limiting coverage to patients who are refractory to standard therapy as

defined in the Phase 3 trial. While it is possible to tailor step therapy in a clinically responsible fashion, it is often administered with documentation burdens and inadequate procedures for exceptions that make step therapy a source of great frustration and the cause of poor outcomes for some patients due to the discontinuation of medicine/missed doses.

For efgartigimod, many payers will follow the clinical trial eligibility criteria as the sole basis for step therapy, but some payers may consider instituting step therapy through immunosuppressive agents, as they do for eculizumab, even though efgartigimod was not tested in a specifically refractory population. Clinical experts accustomed to using immunosuppressive treatments and IVIG prior to eculizumab may not find this approach unreasonable, but clinical experts advising ICER noted that some patients cannot safely use chronic corticosteroids, and steroid sparing agents (mycophenolate and azathioprine for instance) take six to 12 months to work. Therefore, payers should consider creating an explicit pathway for early coverage with eculizumab or efgartigimod for patients who have failed IVIG and corticosteroids, or who cannot take the latter, while waiting for an immunosuppressive agent to take effect.

Manufacturers

Manufacturers should set prices that will foster affordability and good access for all patients by aligning prices with the patient-centered therapeutic value of their treatments. In the setting of these new interventions for gMG, there remains substantial uncertainty regarding their longer-term safety and effectiveness. Manufacturer pricing should reflect these considerations in more moderate launch pricing.

The price for eculizumab is extremely high and is distinctive for the amount by which it exceeds the price needed to reach traditional cost-effectiveness thresholds in the US. Eculizumab was first approved for paroxysmal nocturnal hemoglobinuria and hemolytic uremic syndrome, ultra-rare conditions with a cumulative prevalence of less than 4 per million. The population with gMG is 14-20 per 100,000, and if only 15% of this population is considered to have refractory gMG, the population now eligible for treatment with eculizumab is more than seven times as large as when the drug was first approved, yet the price has not come down. There is no excuse for this level of pricing, and it should not be used as a benchmark or standard for future therapies in this clinical area or others.

Pricing is not just a matter of cost. It is a matter of harm to patients and others throughout the health system. Drug prices that are set well beyond the cost-effective range cause not only financial toxicity for patients and families using the treatments, but also contribute to general health care cost growth that pushes families out of the insurance pool, and that causes others to ration their own care in ways that can be harmful. Prices should not be set based on historical pricing for therapies that are more expensive to produce or have been priced beyond their value to patients.

Manufacturers should therefore price novel treatments in accordance with the demonstrated benefits to patients. In settings of substantial uncertainty, initial pricing should err on the side of being more affordable. This would allow more patients access, generating additional data on the real-world effectiveness of novel treatments that could be used in future assessment updates. With accumulation of evidence of substantial patient benefit, manufacturers should be allowed to increase pricing in accordance with benefit.

Clinicians and Clinical Societies

Clinical specialty societies should continue to bear witness to the impact of high prices for novel therapies on patients.

Doctors need to engage with affordability and pricing as it affects their patients. The AAN has been a leader in highlighting these issues for patients that their clinicians care for, through public outreach including a formal position statement on Ethical Perspectives on Costly Drugs and Health Care,[2] the Neurology Podcast, and statement to the California Technology Assessment Forum on the FDA approval of aducanumab.

Patient Organizations

Patient organizations have a vital role to play by complementing existing clinical research with patient focused surveys collecting data on the impact of gMG on the diversity of patient experiences and the impact on caregivers.

Patient groups continue their efforts to collect data on the impact of gMG on patients and their caregivers. There is a dearth of information on the impacts of gMG on patient and caregiver productivity and importantly on the changes in these measures made by effective therapies. In addition, patient organizations can add important contextual information on the differential impact of gMG on important patient sub-populations such as children, women, and race/ethnicity subgroups. These data could round out the picture on the societal impact of novel therapeutics, which would allow better modeling of both the health care and societal impacts of these therapies.

Researchers/Regulators

Researchers should continue to explore the potential effectiveness of less expensive therapies for patients with gMG.

Many clinicians believe that rituximab can be an effective therapy for patients with gMG, but high-quality comparative effectiveness data have not yet been published, although the results of the BEAT MG study may soon appear. Studies evaluating the effectiveness of maintenance IVIG are also needed to guide clinical practice and insurance coverage.

Researchers should collect data on the larger societal impact of novel therapeutics used to treat patients with gMG, not just the immediate impacts on patients.

Patients told us that managing gMG often led to reduced work hours, decreased responsibilities at work, less income and early retirement for themselves and for their caregivers. Studies of treatments for gMG should collect data documenting changes in missed days of school and work, return to work, and changes in caregiver needs and responsibilities.

References

1. Pearson SD, Towse A, Lowe M, Segel CS, Henshall C. Cornerstones of 'fair' drug coverage: appropriate cost sharing and utilization management policies for pharmaceuticals. *J Comp Eff Res.* 2021;10(7):537-547.
2. Tsou AY, Graf WD, Russell JA, et al. Ethical Perspectives on Costly Drugs and Health Care. *AAN Position Statement.* 2021;97(14):685-692.

Appendix

Appendix Tables 1 through 3 contain conflict of interest (COI) disclosures for all participants at the September 24th Public Meeting of the New England CEPAC.

Table 1. ICER Staff and Consultants and COI Disclosures

ICER Staff and Consultants*	
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Jon Campbell, PhD, MS, Senior Vice President for Health Economics, ICER	**Steven D. Pearson, MD, MSc,** President, ICER
Monica Frederick, Senior Program and Event Coordinator, ICER	**David M. Rind, MD, MSc,** Chief Medical Officer, ICER
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Ashton Moradi, PharmD, MS, Health Economist, ICER	**Daniel R. Touchette, PharmD, MA** University of Illinois at Chicago College of Pharmacy
Dmitriy Nikitin, MSPH, Research Lead, Evidence Synthesis, ICER	

*No conflicts of interest to disclose, defined as individual health care stock ownership (including anyone in the member's household) in any company with a product under study, including comparators, at the meeting in excess of $10,000 during the previous year, or any health care consultancy income from the manufacturer of the product or comparators being evaluated.

Table 2. New England CEPAC Panel Member Participants and COI Disclosures

Participating Members of New England CEPAC*	
Austin Frakt, PhD, Director, Partnered Evidence-Based Policy Resource Center, VA Boston Healthcare System; Professor, Boston University School of Public Health	**Tara Lavelle, PhD,** Assistant Professor, Center for the Evaluation of Value and Risk in Health at Tufts Medical Center
Marthe Gold, MD, MPH, Logan Professor Emerita, CUNY School of Medicine	**Greg Low, RPh, PhD,** Program Director, MGPO Pharmacy Quality and Utilization Program
Megan Golden, JD, Co-Director, Mission:Cure	**Aaron Mitchell, MD, MPH,** Assistant Attending, Memorial Sloan Kettering Cancer Center
Rebecca Kirch, JD, Executive Vice President, Health Care Quality and Value for the National Patient Advocate Foundation (NPAF)	**Brian O'Sullivan, MD,** Professor of Pediatrics, Geisel School of Medicine, Dartmouth College
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Donald Kreis, JD, Consumer Advocate, New Hampshire Office of the Consumer Advocate	

*No relevant conflicts of interest to disclose, defined as more than $10,000 in healthcare company stock or more than $5,000 in honoraria or consultancies during the previous year from health care manufacturers or insurers.

Table 3. Policy Roundtable Participants and COI Disclosures

Policy Roundtable Participant	Conflict of Interest
Adrejia Boutté, JD, Patient Expert	No financial conflicts to disclose
Marcia Lorimer, MSN, CPNP, Board Chair Emerita, Myasthenia Gravis Foundation of America	The MGFA receives >25% of its funding from health care companies, including Alexion and argenx.
Kimberly Grant, PharmD, Clinical Pharmacist, IPD Analytics	Dr. Grant is a full-time employee of IPD Analytics.
Pushpa Narayanaswami, MD, Vice-Chair, Clinical Operations, Beth Israel Deaconess Medical Center; Associate Professor of Neurology, Harvard Medical School	Dr. Narayanaswami has received funding in excess of $5,000 from argenx and UCB, and has received research support from Momenta/Janssen, Alexion, and UCB.
Glenn A. Phillips, PhD, Senior Director, Health Economics and Outcomes Research, argenx	Dr. Phillips is a full-time employee of argenx.
A. Gordon Smith, MD, Professor and Chair of Neurology, Virginia Commonwealth University	Dr. Smith has received funding in excess of $5,000 from Alexion, argenx, Eidos, and Lexicon.
Emily Tsiao, PharmD, Clinical Pharmacist, Premera Blue Cross	Dr. Tsiao is a full-time employee of Premera Blue Cross.