



Oral and Monoclonal Antibody Treatments for Relapsing Forms of Multiple Sclerosis: Final Policy Recommendations

February 21, 2023

Policy Recommendations

Introduction

The following policy recommendations reflect the main themes and points made during the policy roundtable discussion at the January 20, 2023 New England CEPAC public meeting on the use of oral and monoclonal antibody treatments for multiple sclerosis (MS). At the meeting, ICER presented the findings of its revised report on these treatments and New England CEPAC 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 all effective treatment options for patients with RMS, including off-label use of rituximab, are utilized in ways to help improve affordability and access and reduce health inequities.

Over the past two decades, the treatment landscape for RMS has changed dramatically. Currently there are about 20 FDA-approved DMTs available, from modestly effective injectable and oral drugs to highly effective monoclonal antibody infusions and injections. Clinical experts and persons with MS highlighted that since RMS is a heterogenous disease and adherence to DMT can dramatically decrease the risk of relapses and progression of disease, access to effective and affordable treatments is crucial to prevent lifelong disability.

More recent evidence supports that many patients benefit from therapy with highly effective DMTs from the onset of or at worsening of disease. Ublituximab, a monoclonal antibody infusion that was

recently approved by the FDA, joins natalizumab, ocrelizumab, ofatumumab and rituximab as options for patients requiring a highly effective DMT for treatment. Our review found that based on current randomized trial evidence, there is no evidence to distinguish amongst the monoclonal antibodies in terms of their impact on ARR and disability progression. Although biosimilar rituximab has not been specifically studied in RCTs in people with RMS, based on its demonstrated bioequivalence to rituximab and real-world evidence of efficacy,^{1,2} it has been used both in the US and Europe as a first-line treatment option.^{3,4} It is also significantly cheaper than the other monoclonal antibodies. However, because rituximab does not have an FDA-label for MS, some payers are reluctant to cover it for treatment for MS. Thus, many patients do not have access to this more affordable option. All stakeholders should work together to remove barriers to rituximab for the treatment of RMS, as broader use of rituximab, particularly biosimilar rituximab, could lead to better health outcomes, less financial toxicity to patients, and lessen health inequities.

To address these concerns:

Payers should consider the following actions:

- Payers should remove barriers to access to rituximab for RMS patients who are appropriate candidates for this therapy. This includes coverage of biosimilar rituximab with little or no prior authorization given the lack of concern regarding use in appropriate patients and how inexpensive it is compared with other monoclonal antibodies of equal effectiveness. Payers should not be swayed by rebates for more expensive, branded monoclonal antibodies when tiering these drugs.
- Payers should not unilaterally implement policies to switch RMS patients who are stable on their chosen DMT over to lower-cost biosimilar rituximab. Switching to rituximab has not been tried on a systematic basis outside of the Kaiser Permanente system. Kaiser Permanente Southern California has published data from their MS Treatment Optimization Program (MSTOP)⁴ that switching can be done successfully, leading to lower expenditures and better patient outcomes. But this program involves extensive coordination and communication with clinicians and patients, is not mandatory, and payers should understand that many clinicians and patients in other settings will feel that there are unacceptable risks in switching DMTs when patients are stable. There are also heightened medical appeal and legal risks given that rituximab is off label for MS. It is not unreasonable for payers to consider working in collaboration with providers to develop a program similar to that at Kaiser, especially if it is envisioned as an opt-in choice for patients, but otherwise formal coverage requirements to switch to rituximab are inadvisable despite the potential short-term cost savings.

Plan sponsors should take the following actions:

- Plan sponsors should push payers administering their benefit to prioritize coverage of rituximab to help expand access and lower costs for patients who are appropriate for this therapy.
- Plan sponsors should require specialty pharmacy carveouts to share data back with health plans so that they have data across both pharmacy and medical benefit that facilitates more effective and less burdensome utilization management. For example, in RMS, since patients may be treated with both oral medications and infusions, a complete medication history is helpful in determining the appropriateness of coverage for subsequent treatments.

Clinical specialty societies and clinicians should take the following actions:

- Clinical specialty societies such as the American Academy of Neurology should update their guidelines to make clear that off-label rituximab is a reasonable first option for treatment of RMS along with other monoclonal antibody DMTs. Payers expressed the need for clinical guidelines to make an explicit recommendation for the use of rituximab in order for them to provide coverage at least on par with other monoclonal antibodies with an FDA label for RMS.
- Clinical specialty societies should include information on rituximab and biosimilar rituximab, including efficacy, harms, and cost, in any educational materials developed and disseminated to assist clinicians and patients in the shared decision-making process for choosing a DMT.
- Clinicians should advocate for greater coverage of rituximab and its biosimilars by payers given the clinical trial and real-world evidence available to support the use of rituximab in MS. If rituximab is covered, clinicians should explore with patients on an individual basis whether switching to a lower cost DMT option would be in the patient's best interest, following the example of the MSTOP program at Kaiser Southern California.

Patient groups should take the following actions:

- Partnering with clinical specialty societies, patient groups should recognize that they have an important voice in expanding knowledge regarding the option of lower-cost off-label treatments when there is adequate evidence of equivalent effectiveness at lower cost.

Payers

Payers should ensure that savings from lower cost biosimilars and generic formulations are shared with patients through the alignment of copay and coinsurance charges. Specifically, all fairly priced drugs should be placed on the lowest relevant tier and cost sharing for generic drugs with a lower net price must not trigger a higher out-of-pocket cost to the patient compared with branded drugs.

When branded drugs enter the market, copayment assistance programs are often offered to commercially insured patients to assist with copay or coinsurance charges, helping reduce out-of-pocket costs to the patient. However, when a generic medication is introduced, particularly a specialty generic medication such as those for MS, out-of-pocket costs for patients can actually increase due to the placement of the medication on a specialty tier and the lack of manufacturer patient assistance for generic medications. Payers need to take manufacturer patient assistance programs and rebates into consideration when determining tiering for generic drugs so that patients do not end up paying more due to the loss of manufacturer assistance.

Payers should negotiate with providers to minimize drug markups that can drive overuse of more expensive drugs when there are cheaper, equally effective alternatives.

Drug markups are a major driver of provider-administered drug costs. High efficacy treatments for RMS such as monoclonal antibodies that are infusions are subject to markups from hospitals and physician offices, and these markups substantially increase the price of therapy and create incentives for utilization of more expensive drugs in more expensive sites of care. For example, the average markup for a single treatment of ocrelizumab in 2018-2020 was \$4,433 for infusion in a physician's office and \$19,803 for infusion in a hospital setting.⁵ Payers should negotiate to lower drug markup and may consider the use of carefully crafted white bagging and site of service policies that have adequate safeguards including robust exceptions procedures.

Prior Authorization

Given the number of treatment options available for MS, it is reasonable for payers to use prior authorization as a component of coverage for some or all drugs covered. Prior authorization criteria for drugs should be based on clinical evidence and input from clinical experts and patient groups. The process for authorization should also be clear, accessible, efficient, and timely for providers. Perspectives on specific elements of cost-sharing and coverage criteria within insurance coverage policy are discussed below. Relevant [Fair Access Design Criteria](#) set out in ICER's previous work are included.

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 judged to have equivalent overall net health benefits and 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. Specifically, for conditions such as RMS, where there are multiple treatments available, the definition of a “drug class” should be based on clinical expert opinion and clinical practice guidelines.

Coverage Criteria: General

ICER has previously described [general criteria for fair coverage policies](#) that should be considered as cornerstones of any drug coverage policy.

Drug-Specific Coverage Criteria: Ublituximab

Payers should understand that over the past decade, the treatment paradigm for RMS has shifted due to evidence that many patients with RMS benefit from first-line treatment with highly effective DMTs. Thus, some payers may deem it reasonable to minimize the burden of prior authorization for their preferred agents in this class, particularly low-cost biosimilar rituximab.

Given that monoclonal antibody drugs in this class have comparable efficacy but differing administration and side effect profiles, payers should ensure access to multiple DMTs in the class to allow for switching as needed. For example, natalizumab is not recommended for women who are trying to conceive due to the risk of disease reactivation upon discontinuation. However, given that evidence does not suggest distinctive added benefit with ublituximab compared to other monoclonal antibodies, payers are extremely likely to apply prior authorization policies as part of coverage.

Whatever coverage criteria are considered, none should undermine the tenets of fair access to which all patients have a fundamental right. 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 ublituximab.

Coverage Criteria

- **Age:** Age criteria are likely to follow the FDA label for ublituximab and include all adults with RMS.
- **Clinical Eligibility**

Diagnosis: Clinical trials for ublituximab have eligibility criteria requiring diagnosis with RMS by 2017 McDonald Criteria, with more than one relapse per year, and baseline EDSS scores of 5.5 or lower. However, clinical experts indicated that one of the main goals of treatment of RMS is to prevent disability progression and given the efficacy of DMTs in preventing progression, the clinical trial criteria should not be used to define eligible patients for insurance coverage. Specifically:

- The McDonald Criteria are used in clinical trials to ensure that only patients with RMS are included in the trials. Clinical experts felt that a diagnosis of RMS by a neurologist is sufficient to start treatment.
- Clinical experts did not think it is useful to define “active” disease, since relapses alone are not fully indicative of disease activity. Thus, there should not be a minimum number of relapses required to start therapy.
- There is disagreement amongst clinical experts on whether and when it is safe and appropriate to stop DMT. Thus, there should be no age or EDSS cutoff for therapy.

Exclusion Criteria: Ublituximab can reactivate hepatitis B infection and thus it is contraindicated in patients with active hepatitis B. Other clinical trial exclusion criteria should not be used; those criteria are defined for research purposes only and do not necessarily apply to clinical practice.

- **Duration of Coverage and Renewal Criteria:** Although for specialty drugs, initial coverage is usually limited to six to 12 months, for RMS patients, this has limited applicability because there is no clinical consensus on whether and when it is safe to step down to a moderate efficacy DMT or stop DMT and stopping DMT could in some cases lead to disease exacerbations. Thus, clinicians and patients are best suited to assess whether the patient should continue treatment, and even clinician attestation of benefit is viewed as superfluous by clinical experts.
- **Provider Restrictions:** Clinical experts agreed that it is reasonable to restrict prescriptions for ublituximab to neurologists.

- **Step Therapy:** Clinical practice guidelines and clinical experts agree that highly effective DMTs such as ublituximab are considered first-line therapy. Thus, payers should not require step therapy through moderate efficacy medications (e.g., fingolimod, dimethyl fumarate). Payers who do have step therapy through a moderate efficacy DMT and do not allow access to rituximab for RMS should realize that this policy is not consistent with current clinical practice, especially with emerging evidence that many patients have better outcomes with highly effective therapy. Payers should also realize that biosimilar rituximab could provide the benefits of a highly effective DMT at a much lower cost. Thus, coverage of biosimilar rituximab could be a preferable strategy to step therapy.

Manufacturers

Manufacturers should seek to 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 new interventions for MS that are similar in efficacy and safety to other treatments, manufacturer pricing should reflect these considerations in moderating launch pricing.

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.

Manufacturers should therefore price new treatments in accordance with the demonstrated benefits to patients. In the setting of new treatments that do not represent a novel mechanism of action and do not show substantial benefit over comparator treatments, manufacturers should recognize that if pricing were better aligned with value, payers would provide increased access to such treatments.

Additionally, when generic medications and biosimilars are available, manufacturers should recognize that if they are serious about their commitment to improving access to patients, they should not use generics and biosimilars to increase the cost of existing treatments.

Patient Organizations

Patient organizations have a powerful voice and should apply it to create significant pressure for fair pricing and appropriate insurance coverage across all sectors of the health system. In particular, patient organizations should follow the model set by the National MS Society in issuing statements and advocating for fair pricing and access to treatments.

Patient groups should accept responsibility to publicly promote access and fair pricing of new therapies. The National MS Society has been a leader in this area. For example, the Society has issued recommendations to ensure that that access to treatment is affordable, simple, and transparent, including calls to limit price increases for medications that have been on the market for a considerable time; proposing that prior authorization should happen before the person with MS leaves the doctor’s office; and advocating for easily accessible, understandable, and searchable formulary coverage.⁶

Patient groups should additionally follow-up such statements with organized campaigns to advocate for fair pricing, for example, by encouraging patients and families to write to Congress or launch public relation campaigns with such messaging.

Manufacturers, Regulators, Researchers, and Patient Organizations

Support the development of improved measures of disease severity and outcomes that are consistent across trials and meaningful to patients.

Clinical experts identified the lack of standard definitions of disease progression in RMS as a challenge to comparing treatments. We also heard from patient advocacy groups that endpoints used in clinical trials do not always measure what is most important to patients and families. For example, the primary endpoint in most trials is the ARR; however, clinicians and patients are most concerned about preventing the progression of disability. Many trials are not adequately powered or lengthy enough to detect differences in disability, although simply making trials longer may not be in patients’ best interest. In addition, definitions of disease progression differ across trials (e.g., some trials define progression as an increase in EDSS score of 0.5; others define it as an increase of 1.0). Furthermore, trials often measure the endpoints at different times, hindering efforts to do indirect comparisons across trials. Collaboration between manufacturers, regulators, researchers, and patient organizations is essential to define a core set of severity and outcome measures and then promote their implementation in all clinical trials.

Support and advocate for increased diversity of enrollees in clinical trials, particularly since the burden of MS in racial and ethnic populations has been underrecognized.

Currently, clinical trials for RMS recruit mainly White populations. Epidemiological studies have demonstrated that prevalence of MS varies by age, race, ethnicity, and sex, with White and Black individuals having a similar prevalence overall, but Black and Hispanic young adults having a higher prevalence than Whites and Asians among 18-24 year olds.⁷ Additionally, differences in outcomes have been observed amongst patients with MS, although it is not entirely clear whether the differences are due to differences in disease characteristics or course or due to inequities in the health care system such as poorer access to care. Since it is critical for clinical trials to adequately represent the diversity of the US to help answer such questions, sponsors of clinical trials, in

partnership with researchers and patient organizations, should seek systematic ways to recruit diverse populations, e.g., establishing meaningful long-term relationships with community partners, having multicultural recruitment teams, designing culturally sensitive and inclusive recruitment materials, etc.

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Appendix

Tables 1 through 3 contain conflict of interest (COI) disclosures for all participants at the New England CEPAC public meeting on January 20, 2023.

Table 1. ICER Staff and Consultants and COI Disclosures

ICER Staff and Consultants	
Foluso Agboola, MBBS, MPH,* Vice President of Research, ICER	Grace A. Lin, MD,* Medical Director for HTA, ICER; Professor of Medicine and Health Policy, UCSF
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*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. Policy Roundtable Participants and COI Disclosures

Policy Roundtable Participant	Conflict of Interest
Bruce Cohen, MD, Professor of Neurology, Northwestern Feinberg School of Medicine/Northwestern Medicine	Dr. Cohen has equity interests in Abbott Laboratories, AbbVie, and CVS Health. He also served as a site PI for the OPERA trial of ocrelizumab funded by Northwestern University.
David Dohan, MD, Medical Director, Pharmacy, Point32Health	Dr. Dohan is an employee at Point32Health.
Lauren Hirschfeld, Person Living with MS; District Activist Leader, National MS Society	No conflicts of interest to disclose.
Annette Langer-Gould, MD, PhD, Regional Lead, Translational Neuroscience, Southern California Permanente Medical Group	Dr. Langer-Gould served as the site PI for ocrelizumab in the relapsing-remitting Phase III trial. Dr. Langer-Gould also served as the Assistant Medical Director at Genentech from September 2006 – September 2007, where she oversaw the rituximab and ocrelizumab development programs.
William Rose, MBA, Executive Director, Access Marketing and Health Economics Outcomes Research, TG Therapeutics	William is an employee at TG Therapeutics.
Bari Talente, JD, Executive Vice President, Advocacy and Healthcare Access, National MS Society	No conflicts of interest to disclose.
Daniel Uting, PharmD, Senior Clinical Pharmacist, Utilization Management Strategy, Prime Therapeutics	Dr. Uting is an employee at Prime Therapeutics.

Table 3. CTAF Panel Member Participants and COI Disclosures

Participating Members of New England CEPAC*	
<p>Robert H. Aseltine, Jr., PhD* Professor and Chair, Division of Behavioral Sciences and Community Health Director, Center for Population Health, UCONN Health</p>	<p>Aaron Mitchell, MD, MPH* Assistant Attending, Memorial Sloan Kettering Cancer Center</p>
<p>Rena Conti, PhD* Associate Research Director, Biopharma and Public Policy, Institute for Health System Innovation and Policy; Associate Professor, Questrom School of Business</p>	<p>Eleftherios Mylonakis, MD, PhD, FIDSA* Chief, Infectious Diseases Division; Dean’s Professor of Medicine, Warren Alpert Medical School of Brown University</p>
<p>George Goshua, MD, MSc* Assistant Professor of Medicine (Hematology), Yale University School of Medicine</p>	<p>Stephanie Nichols, PharmD, BCPS, BCPP, FCCP* Associate Professor of Pharmacy Practice, University of New England College of Pharmacy; Psychiatric and Substance Use Disorder Pharmacist, Maine Medical Center</p>
<p>Rebecca Kirch, JD* Executive Vice President, Health Care Quality and Value for the National Patient Advocate Foundation</p>	<p>Jeanne Ryer, MSc, EdD* Director, New Hampshire Citizens Health Initiative</p>
<p>Stephen Kogut, PhD* Professor of Pharmacy Practice, University of Rhode Island College of Pharmacy</p>	<p>Jason Wasfy, MD, MPhil* New England CEPAC Chair; Director, Quality and Outcomes Research, Massachusetts General Hospital Heart Center</p>
<p>Greg Low, RPh, PhD* Program Director, MGPO Pharmacy Quality and Utilization Program</p>	<p>Albert Whitaker, MA, MPH* Interim Pastor, St. Mark Congregational Church Consultant, Health Integration and Equity</p>

*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.