



Belimumab and Voclosporin for Lupus Nephritis: Final Policy Recommendations

April 16, 2021

Policy Recommendations

Introduction

The following policy recommendations reflect the main themes and points made during the Policy Roundtable discussion at the March 26, 2021 New England CEPAC public meeting on the use of belimumab and voclosporin for the treatment of lupus nephritis. 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, one patient advocate, and two representatives from pharmaceutical manufacturers 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 lupus nephritis are introduced in a way that will help reduce health inequities.

People from diverse racial and ethnic backgrounds are at a higher risk of developing lupus and lupus nephritis. Unfortunately, patients from these communities are also at a higher risk of not receiving adequate education about their condition, face a longer time between diagnosis to initiation of any therapy, and are often late to receive guidance regarding new treatment options. All stakeholders should accept and act upon their responsibility to address these disparities.

- Manufacturers should engage with a variety of people from diverse communities to help inform the design and implementation of clinical trials, ensure that patients enrolled in pivotal trials are fully representative of people of color and those from less advantaged backgrounds, and should commit to designing trials that capture the comprehensive set of patient outcomes that matter most to patients. It is important that manufacturers not engage the same limited number of individuals to provide input and represent the trials from early design stages through post-marketing roles as ambassadors.
- Payers should engage with people from diverse LN patient groups and with clinical experts in order to infuse coverage policies with sensitivity to the way that different treatments may offer distinct advantages or disadvantages for people based on their social background and living situation. In addition, out-of-pocket financial burden should be scaled to ensure that patients can afford the many drugs that they are frequently required to take for SLE and LN. Health plans should also consider establishing an internal quality assessment measure to seek to maximize the percent of eligible patients with LN who are on belimumab or voclosporin and demonstrating adherence to their medication.
- Patient advocacy groups for people with LN should seek to represent diverse perspectives, requiring outreach to patients who are often not engaged by academic health systems, manufacturers, or other policymakers. Patient groups should collaborate with organizations and people in diverse communities to help build the trust needed to empower all patients and caregivers.
- Clinicians should follow the principle of shared decision-making to ensure that the values of patients with diverse needs and perspectives on risks and benefits of different treatments are at the heart of all treatment decisions.

Payers

Both belimumab and voclosporin are judged to be priced in reasonable alignment with estimates of their benefits for patients, and this consideration should guide payers to design coverage criteria that do not narrow coverage from the FDA label, although coverage criteria may define terms left indeterminate in the FDA label to assure appropriate use.

Given the significant uncertainty that remains about the longer-term safety and effectiveness of belimumab and voclosporin for lupus nephritis, it is reasonable for payers to use prior authorization as a component of coverage. Prior authorization criteria for both 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 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:
- Considered limitations of evidence due to systemic under-representation of minority populations; and
- 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
- 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 the initial request for coverage is denied, access to a peer-to-peer call should be rapid. Management of lupus nephritis 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 in the management of lupus nephritis. If the peer-to-peer call results in the patient receiving the clinician's recommended drug, there should not be a requirement for the renewal review to occur in a short timeframe such as six months, annually is more reasonable.

Drug-Specific Considerations: Belimumab

FDA Label: Adult patients with active LN who are receiving standard therapy.

Coverage Criteria

- **Diagnosis:** Clinical experts advised that renal biopsy is routine for diagnosis but that it would not be reasonable to require a repeat biopsy if one had been previously done within the previous six-month to two-year period. In particular, repeat biopsies are not necessary in the setting of an acute flare of LN in a patient with prior biopsy-proven disease. Clinical experts noted that in some cases the diagnosis seems clear based on worsening proteinuria and/or extra-renal disease, and that some patients may have co-morbidities making biopsy more dangerous, therefore payers may consider having no biopsy requirement or a rapid pathway for medical exceptions.
- **Patient Eligibility Criteria:** Patients should be receiving standard therapy, which consists of concomitant treatment with corticosteroids and MMF or cyclophosphamide. Successful treatment may allow patients to minimize or even eliminate steroid use.
- **Exclusion Criteria:** Patients who had failed both MMF and cyclophosphamide induction, and patients with eGFR < 30 were excluded from the BLISS-LN pivotal trial. However, clinical experts did not believe that eGFR < 30 should be used as a rigid exclusion given that this test result should be viewed in the context of renal biopsy results. Payers may receive requests for dual therapy with belimumab and voclosporin. Although there are pathophysiological arguments for dual therapy, clinical experts agreed that studies are needed to evaluate the outcomes of dual therapy before routine consideration within clinical practice.
- **Duration of Therapy and Renewal of Coverage:** Because belimumab appears to have no risk of nephrotoxicity, and because it may be useful in addressing other symptoms of SLE, payers may opt to require no demonstration of benefit or time limit on initial coverage. Physician attestation of a response to therapy of at least a 50% reduction in proteinuria after 6 to 12 months of therapy is a reasonable consideration.
- **Provider Criteria:** The therapy should be prescribed by a rheumatologist or nephrologist with expertise in LN or, at minimum, access to consultation with an expert. Virtual consultation with a SLE expert at a Lupus Center of Excellence should be supported.

Step Therapy

There is no other treatment that could be considered a first-step treatment prior to eligibility.

Drug-Specific Considerations: Voclosporin

FDA Label: Adult patients with LN in combination with a background immunosuppressive therapy regimen...If the patient has not experienced therapeutic benefit by 24 weeks, consider discontinuation...Consider risks and benefits of treatment beyond one year.

Coverage Criteria

- **Diagnosis:** Clinical experts advised that renal biopsy is routine for diagnosis but that it would not be reasonable to require a repeat biopsy if one had been previously done within the previous six-month to two-year period. In particular, repeat biopsies are not necessary in the setting of an acute flare of LN in a patient with prior biopsy-proven disease. Clinical experts noted that in some cases the diagnosis seems clear based on worsening proteinuria and/or extra-renal disease, and that some patients may have co-morbidities making biopsy more dangerous, therefore payers may consider having no biopsy requirement or a rapid pathway for medical exceptions.
- **Patient Eligibility Criteria:** Patients should be receiving standard therapy, which consists of concomitant treatment with corticosteroids and MMF. Successful treatment may allow patients to minimize or even eliminate steroid use.
- **Exclusion Criteria:** Given the FDA label language, payers are likely to restrict coverage if eGFR < 45. However, clinical experts advised that concomitant renal biopsy results may suggest the possibility for patient benefit even with eGFR below this level. Payers may receive requests for dual therapy with belimumab and voclosporin. Although there are pathophysiological arguments for dual therapy, clinical experts agreed that studies are needed to evaluate the outcomes of dual therapy before routine consideration within clinical practice.
- **Duration of Therapy and Renewal of Coverage:** Given the FDA label language, based on the potential for nephrotoxicity with prolonged use, physician attestation of a response to therapy of at least a 50% reduction in proteinuria after 6 to 12 months of therapy is not unreasonable. Current data support one year of therapy, but clinical experts and some trial data suggest that longer treatment duration may be appropriate in individual patients.
- **Provider Criteria:** The therapy should be prescribed by a rheumatologist or nephrologist with expertise in LN or, at minimum, access to consultation with an expert. Virtual consultation with a SLE expert at a Lupus Center of Excellence should be supported.

Step Therapy

There is no other treatment that could be considered a first-step treatment prior to eligibility.

Manufacturers

Manufacturers should commit to expanding their research, both before and after regulatory approval, to include adequate representation of patients with lupus nephritis from Black and other non-white populations.

We heard over and over about the poor outcomes in non-white populations, but the pivotal trials of both therapies did not represent the race/ethnicity distribution of LN in the United States nor were the race/ethnicity subgroups large enough to make meaningful conclusions about the relative efficacy of the therapies in Blacks and other non-white populations. Manufacturers should commit to performing the research needed to help inform more personalized, tailored care for patients from these communities.

Manufacturers should not seek to use common sense dosing algorithms as a tool to gain prolongation of their patents, thereby adding to future health care affordability concerns and reducing the headroom for future innovative therapies.

The addition of a dosing algorithm to the patent protection for voclosporin significantly extended the time during which no generic competition will be possible. This approach of capitalizing upon a dosing algorithm found to lead to improved outcomes makes financial sense for an individual drug maker but creates greater access barriers to care over time for patients with LN and others due to the additional costs seen with drugs that face no generic competition. Manufacturers serious about a long-term commitment to patients will contribute to future innovation and affordability by resisting the temptation to monetize dosing algorithms, especially those that appear self-evident to clinicians.

Specialty Societies

Specialty societies should work with regulators to standardize the primary outcome used in future pivotal trials of therapies for lupus nephritis.

The primary outcome in the pivotal trial of belimumab changed five years after the study began recruiting participants, was a novel measure, and did not correspond to any of the outcomes measured in the pivotal trial of voclosporin. This makes it challenging for clinicians and guideline developers to use the evidence to guide the choice of therapy for patients. There is a substantial evidence base describing short term measures that predict long term good outcomes in lupus nephritis. One of those measures should be defined as the standard primary outcome.

Specialty societies should update their guidelines to include guidance on appropriate use of belimumab and voclosporin and commit the resources to update guidelines more frequently as evidence evolves.

Payers typically base coverage policy on specialty society guidelines. The first two therapies specifically approved by the FDA to treat lupus nephritis are now available for clinicians to prescribe. However, current US rheumatology and nephrology guidelines have not been updated to guide appropriate use of the therapies. In addition, the guidelines should directly address the heterogeneity in the presentation and clinical course of LN by race/ethnicity. Finally, given the likelihood that the FDA will approve several additional new therapies for LN in the next few years, guideline developers should build in a mechanism to update their guidelines annually (e.g., living guidelines). The specialty societies need to examine their conflict-of-interest policies to ensure appropriate input from clinicians familiar with the latest data.

Researchers

Priority should be given to developing biomarkers that can guide the choice of therapy in lupus nephritis.

Many different immunosuppressive therapies are tried in succession when the initial therapy fails to control the disease. There is currently no rationale strategy to guide therapy as there are no biomarkers that predict a good response with one therapy or a poor response with another therapy. This leads to a process of trial and error on the background of declining renal function that can no longer be recovered. Biomarker guided therapy promises to be more effective and less toxic.

Larger observational studies describing long-term outcomes following both complete and partial response are needed.

The available US studies have overlapping survival curves for patients with complete response and those with partial response to therapy. This does not have face validity. Robust evidence on the time to ESRD and the time to death are needed in order to model the impact of treatment of LN over time. Given the heterogeneity of the disease by race/ethnicity, there should be adequate numbers of patients studied to capture differences in disease trajectory by race/ethnicity. These longitudinal observational studies could also capture the side effects of both corticosteroids and non-steroidal immunosuppressive medications.

Appendix

Appendix Tables 1 through 3 contain conflict of interest (COI) disclosures for all participants at the March 26, 2021 Public meeting of the New England CEPAC.

Appendix Table 1. ICER Staff and Consultants and COI Disclosures

ICER Staff and Consultants	
Rick Chapman , PhD, MS, Director of Health Economics, ICER*	Olena Mandrik , PhD, PharmD, MSc, Research Fellow, The University of Sheffield*
James Fotheringham , MD, PhD, Consultant Nephrologist and Honorary Lecturer, The University of Sheffield	Steven D. Pearson , MD, MSc, President, ICER*
Belen Herce-Hagiwara , BA, Research Assistant, ICER*	Praveen Thokala , PhD, MASc, Senior Research Fellow, The University of Sheffield*
Serina Herron-Smith , BA, Research Assistant, Evidence Synthesis, ICER*	Jeffrey A. Tice , MD, Professor of Medicine, University of California, San Francisco*
Maggie Houle , BS, Program and Event Coordinator, ICER*	Melanie Whittington , PhD, MS, Associate Director of Health Economics, ICER*
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*No conflicts of interest to disclose, defined as individual health care stock ownership in any health plan or pharmaceutical, biotechnology, or medical device manufacturers, or any health care consultant income or honoraria from health plans or manufacturers.

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

Participating Members of CEPAC	
Robert Aseltine , PhD, Professor and Chair, UCONN Health*	Greg Low , RPh, PhD, Director, MGPA Pharmacy Quality and Utilization Program, Massachusetts General Hospital*
Rena Conti , PhD, Associate Professor, Boston University*	Eleftherios Mylonakis , MD, PhD, FIDSA, Professor, Alpert Medical School of Brown University*
Marthe Gold , MD, MPH, Senior Scholar, New York Academy of Medicine*	Stephanie Nichols , PharmD, BCPS, BCPP, FCCP, Associate Professor, University of New England College of Pharmacy*
Megan Golden , JD, CEO, Mission: Cure*	Jeanne Ryer , MSc, EdD, Director, NH Citizens Health Initiative*
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Stephen Kogut , PhD, MBA, RPh, Professor, University of Rhode Island College of Pharmacy*	Jason Wasfy , MD, MPhil, Medical Director, Mass General Physicians Organization*

*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.

Appendix Table 3. Policy Roundtable Participants and COI Disclosures

Policy Roundtable Participant	Conflict of Interest
Kathleen Arntsen , BA, President & CEO, Lupus and Allied Diseases Association, Inc.	LADA receives funding from health care related organizations, including Aurinia and GSK, but members associated with LADA are not compensated.
Linda Goler Blount , MPH, President & CEO, Black Women’s Health Imperative	BWHI’s Rare Disease Diversity Coalition receives sponsorship from Aurinia Pharmaceuticals, Inc.
Christele Felix , BS, Chief Operating Officer, LupusChat	No financial conflicts of interest to disclose.
Meggan Mackay , MD, MS, Investigator and Professor of Medicine, The Feinstein Institutes for Medical Research, Northwell Health	Dr. Mackay participates in industry-sponsored clinical trials for lupus nephritis and is reimbursed for subjects recruited and followed.
Jay McKnight , PharmD, BCPS, Vice President, Pharmacy Clinical and Specialty Strategies, Humana Pharmacy Solutions	Dr. Jay McKnight is a full-time employee of Humana.
Simrat Randhawa , MD, MBA, Senior Vice President, Medical and Clinical Affairs, Aurinia Pharmaceuticals, Inc.	Dr. Simrat Randhawa is a full-time employee of Aurinia Pharmaceuticals, Inc.
Brad Rovin , MD, Professor of Medicine and Pathology, Ohio State University Wexner Medical Center	Dr. Brad Rovin is involved in several trials of novel therapeutics for lupus nephritis and is a consultant on the medical/scientific advisory boards to design trials for these therapeutics. His organization receives less than 25% funding from pharmaceutical companies for clinical trials.
Bernard Rubin , DO, MPH, Medical Director, GlaxoSmithKline	Dr. Bernard Rubin is a full-time employee of GlaxoSmithKline.
Emily Tsiao , PharmD, Clinical Pharmacist, Premera Blue Cross	Dr. Emily Tsiao is a full-time employee of Premera Blue Cross.