Reference number(s)
2502-A

STANDARD MEDICARE PART B MANAGEMENT

BENLYSTA (belimumab)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications
Benlysta is indicated for the treatment of:
A. Patients aged 5 years and older with active systemic lupus erythematosus (SLE) who are receiving standard therapy, and
B. Patients aged 5 years and older with active lupus nephritis who are receiving standard therapy.

Limitations of use
The efficacy of Benlysta has not been evaluated in patients with severe active central nervous system (CNS) lupus. Use of Benlysta is not recommended in this situation.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:
A. Initial requests: Medical records (e.g., chart notes, lab reports) documenting the presence of autoantibodies relevant to SLE (e.g., ANA, anti-ds DNA, anti-Sm, antiphospholipid antibodies, complement proteins), or kidney biopsy supporting diagnosis (where applicable).
B. Continuation requests: Medical records (e.g., chart notes, lab reports) documenting disease stability or improvement.

III. EXCLUSIONS

Coverage will not be provided for members with any of the following exclusions:
A. Severe active central nervous system (CNS) lupus (including seizures that are attributed to CNS lupus, psychosis, organic brain syndrome, cerebritis, or CNS vasculitis requiring therapeutic intervention within 60 days before initiation of belimumab) in a member initiating therapy with Benlysta.
B. Member is using Benlysta in combination with other biologics.

IV. CRITERIA FOR INITIAL APPROVAL

A. Systemic lupus erythematosus (SLE)

Authorization of 12 months may be granted for treatment of active SLE when all of the following criteria are met:

1. Prior to initiating therapy, the member is positive for autoantibodies relevant to SLE (e.g., ANA, anti-ds DNA, anti-Sm, antiphospholipid antibodies, complement proteins)
2. The member meets either of the following criteria:
    i. The member is receiving a stable standard treatment for SLE with any of the following (alone or in combination):
        a. Glucocorticoids (e.g., prednisone, methylprednisolone, dexamethasone)
        b. Antimalarials (e.g., hydroxychloroquine)
        c. Immunosuppressants (e.g., azathioprine, methotrexate, mycophenolate, cyclosporine, cyclophosphamide)
        d. Nonsteroidal anti-inflammatory drugs (NSAIDs, e.g., ibuprofen, naproxen)
    ii. The member has a clinical reason to avoid treatment with a standard treatment regimen.

B. Lupus nephritis

Authorization of 12 months may be granted for treatment of active lupus nephritis when all of the following criteria are met:

1. Prior to initiating therapy, the member is positive for autoantibodies relevant to SLE (e.g., ANA, anti-ds DNA, anti-Sm, antiphospholipid antibodies, complement proteins) or lupus nephritis was confirmed on kidney biopsy.
2. Member is receiving a stable standard therapy regimen (e.g., cyclophosphamide, mycophenolate mofetil, azathioprine, corticosteroids) or has a clinical reason to avoid treatment with a standard therapy regimen.

V. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:

A. The member is currently receiving therapy with the requested medication.
B. The requested medication is being used to treat an indication enumerated in Section IV.
C. The member is receiving benefit from therapy. Benefit is defined as disease stability or improvement.

VI. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Benlysta.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. 2019 Update of the EULAR Recommendations for the Management of Systemic Lupus Erythematosus
4. 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus

5. Kidney Disease: Improving Global Outcomes (KDIGO) 2021 Clinical Practice Guideline for the Management of Glomerular Diseases
6. The British Society for Rheumatology guideline for the management of systemic lupus erythematosus
7. Derivation and Validation of Systemic Lupus International Collaborating Clinics (SLICC) Classification Criteria for Systemic Lupus Erythematosus

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Benlysta are covered.

VII. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

The content of the exclusions can be found in the prescribing information.

The British Society for Rheumatology report that ANAs are present in about 95% of SLE patients. If the test for ANAs is negative, there is a low clinical probability of a member having SLE. The presence of anti-dsDNA antibodies, low complement levels or anti-Smith (Sm) antibodies are highly predictive of a diagnosis of SLE in patients with relevant clinical features. Anti-Ro/La and anti-RNP antibodies are less-specific markers of SLE as they are found in other autoimmune rheumatic disorders as well as SLE.

The SLICC group devised alternative classification criteria for lupus. These criteria introduced a requirement for at least one clinical and one immunological criterion and two others from an expanded list of items compared with the ACR criteria. They also allowed biopsy-proven lupus nephritis in the presence of ANA or anti-dsDNA antibodies to be classified as lupus, without the need for other criteria.

THE EULAR/ACR classification criteria for SLE also requires ANA antibodies for the diagnosis of SLE. The diagnosis can be confirmed with a positive ANA at a titer of ≥1:80 on HEp-2 cells or an equivalent positive test at least once. Testing by immunofluorescence on HEp-2 cells or a solid-phase ANA screening immunoassay with at least equivalent performance is highly recommended.

According to the 2019 update of the EULAR recommendations for the management of systemic lupus erythematosus, the goal of treatment should be remission or low disease activity and prevention of flares in all organs. Glucocorticoids can be used at doses and route of administration that depend on the type and severity of organ involvement. In patients not responding to hydroxychloroquine (alone or in combination with GC) or patients unable to reduce glucocorticoids below doses acceptable for chronic use, addition of immunomodulating/immunosuppressive agents such as methotrexate, azathioprine or mycophenolate should be considered. Cyclophosphamide can be used for severe organ-threatening or life-threatening SLE as well as 'rescue' therapy in patients not responding to other immunosuppressive agents. In patients with inadequate response to standard-of-care (combinations of hydroxychloroquine and glucocorticoids with or without immunosuppressive agents), defined as residual disease activity not allowing tapering of glucocorticoids and/or frequent relapses, add-on treatment with belimumab should be considered.

The British Society for Rheumatology indicates that SLE can be managed with corticosteroids, hydroxychloroquine and other antimalarials, methotrexate, and non-steroidal antiinflammatory drugs (NSAIDs). Patients who present with severe SLE, including renal and NP manifestations, need thorough investigation to exclude other etiologies, including infection. Treatment is dependent on the underlying etiology (inflammatory and/or thrombotic), and patients should be treated accordingly with immunosuppression and/or anticoagulation, respectively. Immunosuppressive regimens for severe active SLE involve intravenous methylprednisolone or high-dose oral prednisolone (up to 1 mg/kg/day) to induce remission, either on their

own or more often as part of a treatment protocol with another immunosuppressive drug. Mycophenolate mofetil or cyclosporine are used for most cases of lupus nephritis and for refractory, severe non-renal disease. Biologic therapies belimumab or rituximab may be considered, on a case-by-case basis, where patients have failed to respond to other immunosuppressive drugs, due to inefficacy or intolerance.

VIII. REFERENCES

1. Benlysta [package insert]. Philadelphia, PA: GlaxoSmithKline LLC; February 2023.
2. Fanouriakis A, Kostopoulou M, Alunno A, et al. 2019 Update of the EULAR Recommendations for the Management of Systemic Lupus Erythematosus. *Ann Rheum Dis*. 2019;78:736-745.
3. Aringer M, Costenbader K, Daikh D, et al. 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus. *Ann Rheum Dis.* 2019;78:1151-1159.
4. Rovin BH, Adler SG, Barratt J, et al. Kidney Disease: Improving Global Outcomes (KDIGO) Golmerular Disease Work Group. KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases. Kidney Int. 2021 Oct; 100(4S):S1-S276.
5. Gordon C, Amissah-Arthru MB, Gayed M, et al. The British Society for Rheumatology guideline for the management of systemic lupus erythematosus in adults. *Rheumatology (Oxford)*. 2018; 57(1):e1-e45.
6. Clinical Consult. CVS Caremark Clinical Programs Review: Focus on Rheumatology Clinical Programs. February 2022.
7. Petri M, Orbai A-M, Alarcon GS, et al. Derivation and Validation of Systemic Lupus International Collaborating Clinics (SLICC) Classification Criteria for Systemic Lupus Erythematosus. *Arthritis Rheum*. 2012; 64:2677-2686. URL: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3409311/. Accessed March 22, 2023.