belimumab (Benlysta®)

EOCCO POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: EOCCO112

Description

Belimumab (Benlysta) is a subcutaneously administered human IgG1 lambda monoclonal antibody that inhibits the binding of soluble human B lymphocyte stimulator protein (BLyS) to its receptors on the B cells.

Length of Authorization

- Initial: 12 months
- Renewal: 12 months

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
belimumab (Benlysta)	Systemic Lupus Erythematosus (SLE); Lupus Nephritis (LN)	200 mg/mL syringe	*4 syringes/28 days
		200 mg/mL autoinjector	*4 autoinjectors/28 days

**Does not include loading dose required for LN*

Initial Evaluation

I. **Belimumab (Benlysta)** may be considered medically necessary when the following criteria below are met:
   A. Member is five years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, a rheumatologist or nephrologist; **AND**
   C. **Not** used in combination with other biologic(s)[e.g., rituximab (Rituxan), abatacept (Orencia), voclosporin (Lupkynis)]; **AND**
   D. A confirmed positive autoantibody test [antinuclear (ANA) and/or anti-double-stranded DNA (anti-ds-DNA)]; **AND**
   E. A diagnosis of one of the following:
      1. **Systemic Lupus Erythematosus (SLE)**; **AND**
         i. A SLE Disease Activity Index (SELENA-SLEDAI) score of ≥ 8 supported by documentation in chart notes; **AND**
         ii. Documentation of baseline Physician's Global Assessment (PGA) score; **AND**
         iii. Treatment with **one** standard therapy agent from each category below, has been ineffective, contraindicated, or **ALL** are not tolerated:
            a. Antimalarials (e.g., chloroquine, hydroxychloroquine)
            b. NSAIDs (e.g., ibuprofen, naproxen)
            c. Immunosuppressive (e.g., azathioprine, mycophenolate mofetil, methotrexate); **OR**
      2. Lupus Nephritis (LN); AND
         i. Biopsy indicating class III (focal), IV (diffuse) or V (membranous) LN; **AND**
         ii. Biopsy shows active lesions or active AND chronic lesions; **AND**

iii. Provider attestation indicating medication will be given in combination with mycophenolate for induction and maintenance OR cyclophosphamide for induction followed by azathioprine for maintenance; **AND**

F. Provider attestation indicating member will continue to receive standard therapy (e.g., antimalarials, NSAIDs, immunosuppressives, corticosteroids), unless all are contraindicated or not tolerated

II. Belimumab (Benlysta) is considered investigational when used for all other conditions, including but not limited to:
   A. Severe active central nervous system lupus

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. A diagnosis of **Systemic Lupus Erythematosus (SLE**); **AND**
   A. Member has exhibited improvement or stability of disease symptoms (e.g., reduction in SELENA-SLEDAI score or PGA score); **OR**
IV. A diagnosis of **Lupus Nephritis (LN)**; **AND**
   A. Member has exhibited improvement or stability of disease symptoms (e.g., reduction in proteinuria, improved/stable serum creatinine, reduction in urinary sediment); **AND**
V. **Not** used in combination with other biologic(s); **AND**
VI. Member will continue to receive standard therapy (e.g., antimalarials, NSAIDs, immunosuppressives, corticosteroids), unless all are contraindicated or not tolerated.

Supporting Evidence

I. The safety and efficacy of belimumab (Benlysta) in the pediatric SLE population was studied via the intravenous formulation in an international, randomized, double blind, placebo-controlled, 52-week, trial involving 93 pediatric patients as young as five years of age. The primary efficacy endpoint was the SLE Responder Index (SRI-4) at Week 52; of the 53 randomized participants to the belimumab (Benlysta) arm, the SRI-4 was 53% while the placebo arm was 44% with an odds ratio of 1.49 and 95% CI (0.64, 3.46).
II. FDA approval of belimumab (Benlysta) in pediatric patients with lupus nephritis was based on the extrapolation of efficacy from the intravenous (IV) study in adults with active lupus nephritis, and supported by pharmacokinetic data from IV studies in adults with active lupus nephritis and from pediatric patients with SLE. The estimated Benlysta exposures for pediatric patients were comparable to adults with active lupus nephritis.

III. Belimumab (Benlysta) was shown to be ineffective in seronegative patients, and is therefore only indicated in patients with active SLE who are autoantibody positive (seropositive). Clinical trials in the setting of LN also included patients who are autoantibody positive.

IV. Per label, the use of belimumab (Benlysta) in combination with other biologics has not been studied and is not recommended.

Systemic Lupus Erythematosus (SLE)

V. The safety and efficacy of belimumab (Benlysta) administered subcutaneously were evaluated in a randomized, double-blind, placebo-controlled trial involving 836 patients with SLE. Patients with severe active lupus nephritis and severe active CNS lupus were excluded. The primary efficacy endpoint was the SRI-4 at Week 52; in the belimumab (Benlysta) arm SRI-4 was 61% compared to placebo 48% with an odds ratio of 1.7 and 95% CI (1.3, 2.3).

A. As reported in the trial baseline concomitant medications included corticosteroids (86%), antimalarials (69%), and immunosuppressives (46%, including azathioprine, methotrexate, and mycophenolate). Most patients (approximately 80%) were receiving 2 or more classes of SLE medications.

Lupus Nephritis (LN)

VI. LN is a kidney disease that develops in about 40% of patients with SLE with approximately 10% of patients with LN developing end stage renal disease (ESRD). Kidney failure, dialysis, and kidney transplants are all common in this patient population. Patients with SLE with any sign of kidney involvement (glomerular hematuria and/or cellular casts, proteinuria >0.5 g/24 hours (or spot urine protein-to-creatine ratio (UPCR) >500 mg/g), unexplained decrease in glomerular filtration rate (GFR)) are candidates for kidney biopsy to confirm diagnosis/class of LN, which then guides treatment.

- Class I (minimal mesangial) and Class II (mesangial proliferative): Usually does not need specific immunosuppressive therapy but may be prone to histological transformation to more aggressive disease on repeat biopsy.
- Class III (focal) and Class IV (diffuse): active, chronic classifications at high risk of developing ESRD, thus are targeted populations for immunosuppressive therapies.
- Class V (membranous): presents similar to nephrotic syndrome with subendothelial deposits. Patients with Class III or IV disease may have these deposits and can be classified as Class III or IV in combination with Class V, can also present as pure Class V. Immunosuppressive therapy is indicated.
- Class VI (advanced sclerosing): patients with sclerosing lesions; generally do not respond to immunosuppressive therapy; treatment requires dialysis and/or kidney transplant.

VII. European Renal Association–European Dialysis and Transplant Association (EULAR/ERA–EDTA) 2019 and 2012 American College of Rheumatology guidelines on LN recommend immunosuppressive therapy for LN starting with an induction phase to achieve a renal response, which is recommended for the first six months of treatment, followed by maintenance therapy. Initial (induction) treatment is recommended with mycophenolate mofetil (MMF) or low-dose intravenous cyclophosphamide, both combined with glucocorticoids (pulses of IV methylprednisolone, then oral prednisone). Subsequent long-term maintenance treatment with MMF or azathioprine should follow, with no, or low-dose (<7.5 mg/day) glucocorticoids. If a

patient fails to respond to the first six months of induction therapy, guidelines suggest switching the immunosuppressive agent in combination with glucocorticoid pulse.

VIII. The safety and efficacy of belimumab (Benlysta) in the setting of LN was evaluated in a randomized, double-blind, placebo-controlled trial involving 448 patients with Class III-V LN. Patients with severe active CNS lupus were excluded. The primary efficacy endpoint was renal response (complete or no response) at week 104. Renal response was defined as urinary protein to creatinine ratio of <0.7, eGFR no worse than 20% below the pre-flare value or ≥60 ml per minute per 1.73 m2, and no rescue therapy. In the belimumab (Benlysta) arm renal response was 43% compared to placebo 32.3% with an odds ratio of 1.6 and 95% CI (1.0, 2.3), P= 0.0311.

- All patients included in the trial were on background therapy with mycophenolate mofetil or cyclophosphamide–azathioprine. Patients were 18 years of age and older with antibody positive SLE, ratio of urinary protein to creatinine > 1 or more, biopsy proven LN class III (focal lupus nephritis) or IV (diffuse lupus nephritis) with, or without, coexisting class V (membranous lupus nephritis), or pure class V lupus nephritis within last 6 months. All patients also had biopsy specimens showing active lesions or active and chronic lesions.

Investigational or Not Medically Necessary Uses

I. Severe active central nervous system lupus
   A. Per label, the use of belimumab (Benlysta) in the setting of severe active central nervous system lupus has not been evaluated, and efficacy has not been established; therefore, use is not recommended by the manufacturer in this setting.

References

1. Benlysta [Prescribing Information]. Philadelphia, PA: GlaxoSmithKline. July 2022.
2. Hahn BH, McMahon MA, Wilkinson A, et al. American College of Rheumatology guidelines for screening, treatment, and management of lupus nephritis. Arthritis Care Res (Hoboken). 2012;64(6):797-808.
3. Fanouriakis A, Kostopoulou M, Alunno A, et al. 2019 Update of the EULAR Recommendation for The Management of Systemic Lupus Erethmatosus. Annals of the Rheumatic Diseases 2019;78:736-745. Available at: https://ard.bmj.com/content/78/6/736
4. Lam NC, Ghetu MV, and Bieniek M. Systemic Lupus Erythematosus: Primary Care Approach to Diagnosis and Management. Am Fam Physician. 2016 Aug 15;94(4):284-294. Available at: https://www.aafp.org/afp/2016/0815/p284.html
5. Furie R, Rovin BH, Houssiau F, et al. Two-year, randomized, controlled trial of belimumab in lupus nephritis. N Engl J Med. 2020;383(12):1117-1128.
6. Belimumab and Voclosporin for Lupus Nephritis: Effectiveness and Value. Draft Evidence Report. Institute for Clinical and Economic Review (ICER). January 2021. Available at: https://icer.org/wp-content/uploads/2020/11/ICER_Lupus-Nephritis_Draft-Evidence-Report_012221.pdf
7. Fanouriakis A, Kostopoulou M, Cheema K, et al. 2019 update of the joint european league against rheumatism and european renal association-european dialysis and transplant association (Eular/era-edta) recommendations for the management of lupus nephritis. Ann Rheum Dis. 2020;79(6):713-723.

Policy Implementation/Update:

Action and Summary of Changes	Date
Updated length of authorization	05/2026
Expanded age requirement to five years and older.	10/2022
Added voclosporin (Lupkynis) in examples of biologics that cannot be used in combination with Benlysta	08/2021
Addition of new indication of lupus nephritis and further specified specialist to include nephrologist. Removal of criteria excluding concomitant use of cyclophosphamide	02/2021
Criteria transitioned into policy with the following updates made: addition of supporting evidence and investigational section, removal of active infection question, removal of vaccine question, updated renewal question relating to symptom improvement into one question, and removing specific symptom improvement parameters to be consistent with the market.	11/2019
Previous review	11/2017
Criteria created	09/2017