

# Benlysta® (Belimumab)

**Policy Number:** 2023E0046P  
**Effective Date:** November 1, 2023

[➔ Instructions for Use](#)

Table of Contents	Page
<a href="#">Coverage Rationale</a> .....	1
<a href="#">Applicable Codes</a> .....	2
<a href="#">Background</a> .....	2
<a href="#">Benefit Considerations</a> .....	3
<a href="#">Clinical Evidence</a> .....	3
<a href="#">U.S. Food and Drug Administration</a> .....	6
<a href="#">References</a> .....	6
<a href="#">Policy History/Revision Information</a> .....	8
<a href="#">Instructions for Use</a> .....	8

Related Commercial Policy
<ul style="list-style-type: none"> <li><a href="#">Provider Administered Drugs – Site of Care</a></li> </ul>
Community Plan Policy
<ul style="list-style-type: none"> <li><a href="#">Benlysta® (Belimumab)</a></li> </ul>

## Coverage Rationale

[➔ See Benefit Considerations](#)

This policy refers only to Benlysta (belimumab) injection for intravenous infusion for the treatment of systemic lupus erythematosus (SLE) and active lupus nephritis (LN). Benlysta (belimumab) for self-administered subcutaneous injection is obtained under the pharmacy benefit and is indicated for systemic lupus erythematosus and active lupus nephritis.

**Benlysta (belimumab) is proven and medically necessary for the treatment of systemic lupus erythematosus when all of the following criteria are met:**

- For **initial therapy**, all of the following:
  - Diagnosis of active systemic lupus erythematosus, without severe active central nervous system lupus; **and**
  - Currently receiving at least **one** standard of care treatment for active systemic lupus erythematosus (e.g., antimalarials, corticosteroids, or immunosuppressants) that is not a biologic<sup>7,10</sup>; **and**
  - Patient is not receiving Benlysta in combination with Lupkynis (voclosporin) or Saphnelo (anifrolumab-fnia); **and**
  - Benlysta is initiated and titrated according to US Food and Drug Administration labeled dosing for SLE; **and**
  - Initial authorization is for no more than 12 months.
- For **continuation of therapy**, all of the following:
  - Patient has previously received Benlysta injection for intravenous infusion; **and**
  - Documentation of positive clinical response; **and**
  - Currently receiving at least **one** standard of care treatment for active systemic lupus erythematosus (e.g., antimalarials, corticosteroids, or immunosuppressants; that is not a biologic<sup>1-7,10</sup>; **and**
  - Patient is not receiving Benlysta in combination with Lupkynis (voclosporin) or Saphnelo (anifrolumab-fnia); **and**
  - Benlysta is dosed according to US Food and Drug Administration labeled dosing for SLE; **and**
  - Authorization is for no more than 12 months.

**Benlysta (belimumab) is proven and medically necessary for the treatment of active lupus nephritis when all of the following criteria are met:**

- For **initial therapy**, all of the following:
  - Diagnosis of active lupus nephritis, without severe active central nervous system lupus; **and**

- Currently receiving at least **one** standard of care treatment for active systemic lupus erythematosus (e.g., antimalarials, corticosteroids, or immunosuppressants) that is not a biologic<sup>1-7,10</sup>; **and**
- Patient is not receiving Benlysta in combination with Lupkynis (voclosporin) or Saphnelo (anifrolumab-fnia); **and**
- Benlysta is initiated and titrated according to US Food and Drug Administration labeled dosing; **and**
- Initial authorization is for no more than 12 months.
- For **continuation of therapy**, all of the following:
  - Patient has previously received Benlysta injection for intravenous infusion; **and**
  - Documentation of positive clinical response; **and**
  - Currently receiving at least **one** standard of care treatment for active systemic lupus erythematosus (e.g., antimalarials, corticosteroids, or immunosuppressants); that is not a biologic<sup>1-7,10</sup>; **and**
  - Patient is not receiving Benlysta in combination with Lupkynis (voclosporin) or Saphnelo (anifrolumab-fnia); **and**
  - Benlysta is dosed according to US Food and Drug Administration labeled dosing; **and**
  - Authorization is for no more than 12 months.

**Benlysta is unproven and not medically necessary for:**

- Antineutrophil cytoplasmic antibody-associated vasculitis
- Rheumatoid arthritis
- Severe active central nervous system (CNS) lupus<sup>1</sup>
- Sjögren's syndrome
- Use in combination with other biologics<sup>1</sup>
- Waldenström macroglobulinemia

## Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

HCPCS Code	Description
J0490	Injection, belimumab, 10 mg

Diagnosis Code	Description
M32.0	Drug-induced systemic lupus erythematosus
M32.10	Systemic lupus erythematosus, organ or system involvement unspecified
M32.11	Endocarditis in systemic lupus erythematosus
M32.12	Pericarditis in systemic lupus erythematosus
M32.13	Lung involvement in systemic lupus erythematosus
M32.14	Glomerular disease in systemic lupus erythematosus
M32.15	Tubulo-interstitial nephropathy in systemic lupus erythematosus
M32.19	Other organ or system involvement in systemic lupus erythematosus
M32.8	Other forms of systemic lupus erythematosus
M32.9	Systemic lupus erythematosus, unspecified

## Background

Benlysta (belimumab) is a recombinant human IgG1 $\lambda$  monoclonal antibody specific for soluble human B lymphocyte stimulator protein (BLyS, also referred to as BAFF and TNFSF13B). Belimumab blocks the binding of soluble BLyS, a B-cell survival factor,

to its receptors on B cells. Belimumab does not bind B cells directly, but by binding BLyS, belimumab inhibits the survival of B cells, including autoreactive B cells, and reduces the differentiation of B cells into immunoglobulin-producing plasma cells.

## Benefit Considerations

Some Certificates of Coverage allow for coverage of experimental/investigational/unproven treatments for life-threatening illnesses when certain conditions are met. The member specific benefit plan document must be consulted to make coverage decisions for this service. Some states mandate benefit coverage for off-label use of medications for some diagnoses or under some circumstances when certain conditions are met. Where such mandates apply, they supersede language in the benefit document or in the medical or drug policy. Benefit coverage for an otherwise unproven service for the treatment of serious rare diseases may occur when certain conditions are met. Refer to the Policy and Procedure addressing the treatment of serious rare diseases.

## Clinical Evidence

### Proven

#### *Systemic Lupus Erythematosus*

Belimumab is indicated for the treatment of active, autoantibody-positive, systemic lupus erythematosus (SLE) who are receiving standard therapy.<sup>1</sup>

Ginzler et al evaluated the efficacy/safety of belimumab plus standard therapy in patients (n = 449) with active SLE treated up to 7 years (n = 177, currently ongoing).<sup>14</sup> Patients (n = 345) who completed a double-blind, placebo-controlled, 52-week study of belimumab 1, 4, or 10 mg/kg and 24-week extension of belimumab (placebo switched to 10 mg/kg; belimumab same dose or switched to 10 mg/kg) could receive belimumab 10 mg/kg in an open-label continuation study (n = 296). Disease activity was analyzed in patients with active SLE at baseline of the initial study. Efficacy endpoints measured included percentage change in the Safety of Estrogen in Lupus Erythematosus National Assessment-SLE Disease Activity Index (SELENA-SLEDAI), frequency of 1 new British Isles Lupus Assessment Group (BILAG) A or 2 new B scores, frequencies of mild-moderate and severe flares as defined by SELENA-SLEDAI Flair Index (SFI), and change in corticosteroid use. Total belimumab exposure over 7 years (double-blind<sup>5</sup> and open-label periods<sup>14</sup>) was 1746 patient-years. SLE Responder Index (SRI) response rates reported at Week 52 in autoantibody-positive patients was placebo, 29%; belimumab, 46% (p < 0.05). Researchers reported the following in the continuation study: 57% of auto-antibody-positive patients had an SRI response by Year 2 and 65% by Year 7; severe flares occurred in 19% with placebo and 17% with belimumab during the first year, with the annual rate declining to 2%-9% during years 2-7. Anti-dsDNA autoantibodies in patients positive for them at baseline had a progressive decline of 40%-60% from baseline over 2-7 years with belimumab. Corticosteroid use decreased over time with ≥ 50-55% reduction in median dose during years 5-7. Serious and overall annual AE rates, including infections, were generally stable or decreased during 7-year treatment. Researchers concluded that the data showed that belimumab administered over the long term with standard therapy was generally well tolerated, and sustained disease control was maintained for up to 7 years in patients with active SLE at baseline.

In a post hoc, pooled analysis of the BLISS-52 and BLISS-76 studies, Strand et al assessed the effects of belimumab treatment on health-related quality of life (HRQOL) in patients with active, autoantibody-positive systemic lupus erythematosus (SLE).<sup>17</sup> The authors analyzed data from the major secondary endpoints of the two studies, which were the mean change in SF-36v2 Health Survey Physical Component Summary (PCS) scores at week 24. Additional pre-specified secondary endpoints included mean changes from baseline in Short Form-36 (SF-36) PCS, Mental Component Summary (MCS), and domains, Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) V.4, and EuroQol-5D (EQ-5D) scores at weeks 12, 24, 52 and 76 (BLISS-76 only). The SF-36, FACIT-Fatigue, and EQ-5D were administered at baseline, and weeks 4, 8, 12, 24 and 52 in both trials, and additionally at weeks 20, 32, 40, 48, 68 and 76 in BLISS-76 and week 36 in BLISS-52. Baseline SF-36 scores were 1.5 standard deviations (SDs) below age-/sex-matched US norms with similar improvement at week 24 across treatment groups. Mean changes from baseline in PCS scores were significantly (p < 0.05) greater with belimumab 1 mg/kg (4.20) and 10 mg/kg (4.18) versus placebo (2.96) in BLISS-52, week 52. In BLISS-76, significantly (p < 0.05) greater improvements were seen with belimumab 1 mg/kg in PCS (belimumab 1 mg/kg = 4.37, 10 mg/kg = 3.41 vs placebo = 2.85) and Mental Component Summary (MCS) scores (belimumab 1 mg/kg = 3.14, 10 mg/kg = 2.70 vs placebo = 1.40) at week 52, and in MCS score at week 76 (belimumab 1 mg/kg = 3.05, 10 mg/kg = 2.28 vs placebo = 1.36), however, mean changes in PCS and MCS scores with

belimumab 10mg/kg were not significantly different (week 52: PCS = 3.41, MCS = 2.70, and MCS week 76 = 2.28). In pooled analysis, there were significantly greater improvements in PCS scores with both belimumab doses versus placebo ( $p < 0.05$ ), and MCS scores with 1mg/kg ( $p < 0.01$ ). FACIT-Fatigue scores were not significantly different at week 24, however at week 52, scores improved significantly ( $p < 0.05$ ) with belimumab 1 and 10mg/kg vs. placebo in BLISS-52, and with 1mg/kg at weeks 52 and 76 in BLISS-76. In pooled analysis, FACIT-Fatigue scores were significantly improved ( $p < 0.05$ ) with both dosages at week 52, as well as weeks 8 and 12. EQ-5D utility index and VAS scores were not significantly different between treatment groups in BLISS-52. In BLISS-76, the EQ-5D VAS score was only significantly improved with belimumab 1mg/kg at week 52. The authors concluded that patients receiving belimumab reported clinically meaningful improvements in HRQOL and fatigue versus placebo, in both individual BLISS studies and by pooled analyses, that are consistent with the reductions in disease activity observed in the trials.

## Active Lupus Nephritis

Belimumab is indicated for the treatment of patients aged 5 years of age and older with active lupus nephritis who are receiving standard therapy.<sup>1</sup>

The safety and effectiveness of belimumab 10 mg/kg administered intravenously over 1 hour on Days 0, 14, 28, and then every 28 days plus standard therapy were evaluated in a 104-week, randomized, double-blind, placebo-controlled trial in 448 adult patients with active proliferative and/or membranous lupus nephritis. The patients had a clinical diagnosis of SLE according to American College of Rheumatology classification criteria; biopsy-proven lupus nephritis Class III, IV, and/or V; and had active renal disease at screening requiring standard therapy: corticosteroids with 1) mycophenolate for induction followed by mycophenolate for maintenance, or 2) cyclophosphamide for induction followed by azathioprine for maintenance. This trial was conducted in Asia, North America, South America, and Europe. The mean age of patients was 33 years (range: 18-77); the majority (88%) were female. The primary efficacy endpoint was Primary Efficacy Renal Response (PERR) at Week 104, defined as a response at Week 100 confirmed by a repeat measurement at Week 104 of the following parameters: urine protein: creatinine ratio (uPCR)  $\leq 0.7$  g/g and estimated glomerular filtration rate (eGFR)  $\geq 60$  mL/min/1.73 m<sup>2</sup> or no decrease in eGFR of  $> 20\%$  from pre-flare value. The major secondary endpoints included Complete Renal Response (CRR) defined as a response at Week 100 confirmed by a repeat measurement at Week 104 of the following parameters: uPCR 10% from pre-flare value, PERR at Week 52 and time to renal-related event or death (renal-related event defined as first event of end-stage renal disease, doubling of serum creatinine, renal worsening [defined by quantified increase in proteinuria and/or impaired renal function], or receipt of renal disease-related prohibited therapy due to inadequate lupus nephritis control or renal flare management). The proportion of patients achieving PERR at Week 104 was significantly higher in patients receiving belimumab plus standard therapy compared with placebo plus standard therapy. The major secondary endpoints also showed significant improvement with belimumab plus standard therapy compared with placebo plus standard therapy. Subjects who received BENLYSTA were significantly less likely to experience a renal-related event or death compared with placebo. In descriptive subgroup analyses of time to renal-related event or death, results were consistent with the overall endpoint regardless of induction therapy (mycophenolate or cyclophosphamide), biopsy class (Class III or IV, Class III + V or Class IV + V, or Class V; post-hoc analysis), and baseline proteinuria ( $< 3$  g/g or  $\geq 3$  g/g; post-hoc analysis). The treatment difference was primarily driven by the renal worsening and renal-related treatment failure components of the endpoint.

The safety and efficacy of belimumab 10 mg/kg administered intravenously over 1 hour on Days 0, 14, 28, and then every 28 days plus standard therapy was evaluated in an international, randomized, double-blind, placebo-controlled, 52-week, pharmacokinetics (PK), efficacy and safety study conducted in 93 pediatric patients with a clinical diagnosis of SLE according to the American College of Rheumatology classification criteria. Patients had active SLE disease, defined as a SELENA-SLEDAI score  $\geq 6$  and positive autoantibodies at screening as defined in the adult trials. Patients were on a stable SLE treatment regimen (standard of care) and had similar inclusion and exclusion criteria as in the adult studies. The median age was 15 years (range: 6 to 17). The majority (95%) of patients were female. More than 50% of patients had 3 or more active organ systems involved at baseline. The most common active organ systems at baseline based on SELENA-SLEDAI were mucocutaneous (91%), immunologic (74%), and musculoskeletal (73%). Overall, 19% of pediatric patients had some degree of renal activity and less than 7% had activity in the cardio-respiratory, hematologic, CNS or vascular systems. Randomization into age-related treatment cohorts was stratified by screening SELENA-SLEDAI scores (6 to 12 vs  $> 13$ ) and age (5 to 11 years vs 12 to 17 years). The primary efficacy endpoint was the SLE Responder Index (SRI-4) at Week 52, as described in the adult intravenous trials. There was a numerically higher proportion of pediatric patients achieving a response in SRI-4 and its components in pediatric patients receiving belimumab plus standard therapy compared with placebo plus standard therapy [53% vs. 44%; OR 1.49 (0.64, 3.46)]. A major secondary endpoint, the probability of experiencing a severe SLE flare, as measured by the modified SELENA-SLEDAI Flare Index, excluding severe flares triggered only by an increase of the SELENA-SLEDAI score to  $> 12$ , was

calculated. The proportion of pediatric patients reporting at least one severe flare during the study was numerically lower in pediatric patients receiving belimumab plus standard therapy (17%) compared with those receiving placebo plus standard therapy (35%). Pediatric patients receiving belimumab 10 mg/kg plus standard therapy had a 64% lower risk of experiencing a severe flare during the 52 weeks of observation, relative to the placebo plus standard therapy group. Of the pediatric patients experiencing a severe flare, the median time to the first severe flare was 150 days in pediatric patients receiving belimumab plus standard therapy compared with 113 days in pediatric patients receiving placebo plus standard therapy.

## Unproven

Efficacy of belimumab has not been established in patients with severe active CNS lupus, and belimumab has not been studied in combination with other biologic agents.<sup>1</sup> Therefore, use of belimumab in these situations is unproven.

The use of belimumab is also being investigated for treatment of other conditions, such as, antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis<sup>22</sup>, Waldenström macroglobulinemia<sup>9,16</sup>, Sjögren's syndrome<sup>11</sup>, and rheumatoid arthritis.<sup>12,15</sup> Use of belimumab is considered unproven for these indications due to a lack of large, controlled clinical trials and published evidence demonstrating improved health outcomes.

## Professional Societies

### *The European League Against Rheumatism (EULAR)*

In 2019, EULAR published updated recommendations for the management of systemic lupus erythematosus (SLE). Their recommendations applicable to belimumab are as follows.<sup>18</sup>

## Treatment of SLE

Biologics:

- In patients with inadequate response to standard-of-care (combinations of hydroxychloroquine (HCQ) and glucocorticoids (GC) 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 (1a/A).
- In organ-threatening disease refractory or with intolerance/contraindications to standard immunosuppressive agents, rituximab can be considered (2b/C).

## Neuropsychiatric Lupus

More expansive EULAR guidelines for neuropsychiatric lupus were published in 2010.<sup>19</sup> Treatment guidelines are below:

### *Treatment*

SLE patients with major neuropsychiatric manifestations considered to be of inflammatory origin (optic neuritis, acute confusional state/coma, cranial or peripheral neuropathy, psychosis, and transverse myelitis/myelopathy) may benefit from immunosuppressive therapy.

## Pregnancy In Lupus

Pregnancy affects mothers with SLE and their off-springs in several ways.

### *Mother*

There is no significant difference in fertility in lupus patients. Pregnancy may increase lupus disease activity, but these flares are usually mild. Patients with lupus nephritis and anti-phospholipid antibodies are more at risk of developing pre-eclampsia and should be monitored more closely.

### *Fetus*

SLE may affect the fetus in several ways, especially if the mother has a history of lupus nephritis, antiphospholipid, anti-Ro and/or anti-La antibodies. These conditions are associated with an increase of the risk of miscarriage, stillbirth, premature delivery, intrauterine growth restriction and fetal heart block. Prednisolone, azathioprine, hydroxychloroquine, and low dose aspirin may be used in lupus pregnancies. At present evidence suggests that mycophenolate mofetil, cyclophosphamide and methotrexate must be avoided.

## Anti-Phospholipid Syndrome

In patients with SLE and anti-phospholipid antibodies, low-dose aspirin may be considered for primary prevention of thrombosis and pregnancy loss. Other risk factors for thrombosis should also be assessed. Estrogen-containing drugs increase the risk for thrombosis. In non-pregnant patients with SLE and APS-associated thrombosis, long-term anticoagulation with oral anticoagulants is effective for secondary prevention of thrombosis. In pregnant patients with SLE and anti-phospholipid syndrome combined unfractionated or LMW heparin and aspirin reduce pregnancy loss and thrombosis and should be considered.

## Lupus Nephritis

More expansive EULAR guidelines for lupus nephritis were published in 2012.<sup>20</sup>

Treatment guidelines are below:

### *Treatment*

In patients with proliferative lupus nephritis, glucocorticoids in combination with immunosuppressive agents are effective against progression to end-stage renal disease. Long-term efficacy has been demonstrated only for cyclophosphamide-based regimens, which are however, associated with considerable adverse effects. In short- and medium-term trials, mycophenolate mofetil has demonstrated at least similar efficacy compared to pulse cyclophosphamide and a more favorable toxicity profile: failure to respond by 6 months should evoke discussions for intensification of therapy. Flares following remission are not uncommon and require diligent follow-up.

## End-Stage Renal Disease

Dialysis and transplantation in SLE have comparable rates for long-term patient and graft-survival as those observed in non-diabetic non-SLE patients, with transplantation being the method of choice.

## U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

Benlysta is a B-lymphocyte stimulator (BLyS)-specific inhibitor indicated for the treatment of patients aged 5 years and older with active systemic lupus erythematosus who are receiving standard therapy and patients aged 5 years and older with active lupus nephritis who are receiving standard therapy.<sup>1</sup>

### Limitations of Use<sup>1</sup>

- The efficacy of Benlysta has not been evaluated in patients with severe active central nervous system lupus. Use of Benlysta is not recommended in this situation.

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## Policy History/Revision Information

Date	Summary of Changes
11/01/2023	<p data-bbox="337 220 594 247"><b>Coverage Rationale</b></p> <p data-bbox="337 256 748 283"><b>Systemic Lupus Erythematosus</b></p> <ul data-bbox="337 291 1474 386" style="list-style-type: none"><li>Revised coverage criteria for <b>initial therapy</b>; removed criterion requiring laboratory testing has documented the presence of autoantibodies [e.g., ANA, Anti-dsDNA, Anti-Sm, Anti-Ro/SSA, Anti-La/SSB]</li></ul> <p data-bbox="337 394 643 422"><b>Supporting Information</b></p> <ul data-bbox="337 430 1256 487" style="list-style-type: none"><li>Updated <i>FDA</i> and <i>References</i> sections to reflect the most current information</li><li>Archived previous policy version 2022E0046O</li></ul>

## Instructions for Use

This Medical Benefit Drug Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, please check the member specific benefit plan document and any applicable federal or state mandates. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Benefit Drug Policy is provided for informational purposes. It does not constitute medical advice.

This Medical Benefit Drug Policy may also be applied to Medicare Advantage plans in certain instances. In the absence of a Medicare National Coverage Determination (NCD), Local Coverage Determination (LCD), or other Medicare coverage guidance, CMS allows a Medicare Advantage Organization (MAO) to create its own coverage determinations, using objective evidence-based rationale relying on authoritative evidence ([Medicare IOM Pub. No. 100-16, Ch. 4, §90.5](#)).

UnitedHealthcare may also use tools developed by third parties, such as the InterQual<sup>®</sup> criteria, to assist us in administering health benefits. UnitedHealthcare Medical Benefit Drug Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.