Benlysta® (Belimumab)

Policy Number: 2025E0046S
Effective Date: December 1, 2025

➲ Instructions for Use

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Coverage Rationale

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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, unless otherwise specified in the member's benefit plan documents. Exception: For members enrolled in UnitedHealthcare of California plans with a delegated provider group conducting the prior authorization review, the self-administered Benlysta may be obtained under the medical benefit.

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; **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; **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; **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; **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
- Sjögren's syndrome
- Use in combination with other biologics
- 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 IgG1λ 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.

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.

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). 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[5] and open-label periods) 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). 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.

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) ≤ 0.7 g/g and estimated glomerular filtration rate (eGFR) ≥ 60 mL/min/1.73 m2 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 ≥ 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 ≥ 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. 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, Waldenström macroglobulinemia, Sjögren's syndrome, and rheumatoid arthritis. 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.

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.

Limitations of Use

- 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
12/01/2025	**Supporting Information** • Updated *Clinical Evidence* and *References* sections to reflect the most current information • Archived previous policy version 2025E0046R

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® 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.