Benlysta® (Belimumab)

Policy Number: CS2022D0046T
Effective Date: October 1, 2022

Instructions for Use

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Commercial Policy
• Benlysta® (Belimumab)

Application

This Medical Benefit Drug Policy does not apply to the states listed below; refer to the state-specific policy/guideline, if noted:

State	Policy/Guideline
Florida	Refer to the state's Medicaid clinical policy
Indiana	Benlysta® (Belimumab) (for Indiana Only)
Kansas	Refer to the state's Medicaid clinical policy
Louisiana	Benlysta® (Belimumab) (for Louisiana Only)
North Carolina	None
Texas	Refer to drug specific criteria found within the Texas Medicaid Provider Procedures Manual

Coverage Rationale

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
  - Laboratory testing has documented the presence of autoantibodies [e.g., ANA, Anti-dsDNA, Anti-Sm, Anti-Ro/SSA, Anti-La/SSB]; 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;[1-7,10] and
  - Patient is not receiving Benlysta in combination with Lupkynis (voclosporin) or Saphnelo (anifrolumab-fnia); and
  - Benlysta is initiated and titrated according to U.S. 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;[1-7,10] and
  - Patient is not receiving Benlysta in combination with Lupkynis (voclosporin) or Saphnelo (anifrolumab-fnia); and
  - Benlysta is dosed according to U.S. 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;[1-7,10] 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;[1-7,10] 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[1]
- Sjögren's syndrome
- Use in combination with other biologics[1]
- 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 federal, state, or contractual requirements 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

Diagnosis Code	Description
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.

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.[1]

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).[14] Patients (n = 345) who completed a double-blind, placebo-controlled, 52-week study of belimumab 1, 4, or 10 mg/kg and a 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 one new British Isles Lupus Assessment Group (BILAG) A or two new B scores, frequencies of mild to 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[14]) was 1,746 patient-years. SLE Responder Index (SRI) response rates reported at week 52 in autoantibody-positive patients was placebo 29% and belimumab 46% ($p < 0.05$). Researchers reported the following in the continuation study: 57% of autoantibody-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).[17] 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 U.S. 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 10 mg/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 10 mg/kg vs. placebo in BLISS-52, and with 1 mg/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 1 mg/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 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.[1]

The safety and effectiveness of belimumab 10 mg/kg administered intravenously over 1 hour on days 0, 14, and 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 to 77) and 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, and 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 in 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.[1] 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[22], Waldenström macroglobulinemia[9,16], Sjögren's syndrome[11], and rheumatoid arthritis.[12,15] 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

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.[18]

- 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.[19] 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 offspring 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.[20] 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, autoantibody-positive, systemic lupus erythematosus who are receiving standard therapy and patients aged 5 years and older with active lupus nephritis who are receiving standard therapy.[1]

Limitations of Use[1]

- Benlysta is not recommended in patients with severe active central nervous system lupus.
- Benlysta is not recommended to be used in combination with other biologics.

The efficacy of Benlysta has not been evaluated in patients in these situations.

Progressive Multifocal Leukoencephalopathy (PML)[1]

Cases of JC virus-associated PML resulting in neurological deficits, including fatal cases, have been reported in patients with SLE receiving immunosuppressants, including Benlysta. Risk factors for PML include:

- Testing positive for anti-JC virus (JCV) antibodies
- Longer duration of treatment with immunosuppressant therapies, including Benlysta
- Impairment of immune function

The risks and benefits of continuing treatment with Benlysta should be carefully considered in those patients who are found to be anti-JCV antibody positive and have one or more of these risk factors for PML.

Consider the diagnosis of PML in any patient presenting with new-onset or deteriorating neurological signs and symptoms and consult with a neurologist or other appropriate specialist as clinically indicated. In patients with confirmed PML, consider stopping immunosuppressant therapy, including Benlysta.

A patient's anti-JCV antibody status may be determined using an anti-JCV antibody detection test that has been analytically and clinically validated and has been ordered by a healthcare professional. The Stratify JCV® DxSelect™ Antibody ELISA Test was cleared by FDA on January 20, 2012.[21]

The safety and efficacy of intravenous administration of Benlysta for the treatment of systemic lupus erythematosus has not been established in children younger than 5 years of age. The safety and efficacy of intravenous administration of Benlysta for the treatment of active lupus nephritis has not been established in children younger than 18 years of age. The safety and efficacy of subcutaneous administration of Benlysta has not been established in children younger than 18 years of age.[1]

In phase 3 trials, response rates for the primary endpoint were lower for African American subjects in the Benlysta group relative to African American subjects in the placebo group. Therefore, Benlysta should be used with caution in African American patients.[1]

Benlysta should be administered by healthcare providers prepared to manage anaphylaxis.[1]

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Policy History/Revision Information

Date	Summary of Changes
10/01/2022	**Application** *Texas* • Replaced instruction to "refer to the state's Medicaid clinical policy" with "refer to the drug-specific criteria found within the *Texas Medicaid Provider Procedures Manual*" **Supporting Information** • Updated *Clinical Evidence*, *FDA*, and *References* sections to reflect the most current information • Archived previous policy version CS2022D0046S

Instructions for Use

This Medical Benefit Drug Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the federal, state or contractual requirements for benefit plan coverage must be referenced as the terms of the federal, state or contractual requirements for benefit plan coverage may differ from the standard benefit plan. In the event of a conflict, the federal, state or contractual requirements for benefit plan coverage govern. Before using this policy, please check the federal, state or contractual requirements for benefit plan coverage. 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.

UnitedHealthcare may also use tools developed by third parties, such as the InterQual® criteria, to assist us in administering health benefits. The 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.