Policy Number	**RX501.116**
Policy Effective Date	**08/15/2025**

Belimumab

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Related Policies (if applicable)
None

Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current generally accepted standards of and developed by nonprofit professional association(s) for the relevant clinical specialty, third-party entities that develop treatment criteria, or other federal or state governmental agencies. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and generally accepted standards of medical care. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.

Carefully check state regulations and/or the member contract.

Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Legislative Mandates

EXCEPTION: For HCSC members residing in the state of Ohio, § 3923.60 requires any group or individual policy (Small, Mid-Market, Large Groups, Municipalities/Counties/Schools, State Employees, Fully-Insured, PPO, HMO, POS, EPO) that covers prescription drugs to provide for the coverage of any drug approved by the U. S. Food and Drug Administration (FDA) when it is prescribed for a use recognized as safe and effective for the treatment of a given indication in one or more of the standard medical reference compendia adopted by the United States Department of Health and Human Services or in medical literature even if the FDA has not approved the drug for that indication. Medical literature support is only satisfied when safety and efficacy has been confirmed in two articles from major peer-reviewed professional medical journals that present data supporting the proposed off-label use or uses as generally safe and effective. Examples of accepted journals include, but are not limited to, Journal of

American Medical Association (JAMA), New England Journal of Medicine (NEJM), and Lancet. Accepted study designs may include, but are not limited to, randomized, double blind, placebo controlled clinical trials. Evidence limited to case studies or case series is not sufficient to meet the standard of this criterion. Coverage is never required where the FDA has recognized a use to be contraindicated and coverage is not required for non-formulary drugs.

Coverage

NOTE 1: This policy is specific to belimumab (Benlysta) intravenous use. Self-administered subcutaneous injection is obtained under the pharmacy benefit.

Belimumab (Benlysta®) **may be considered medically necessary** for the treatment of patients aged 5 years and older with:
• Active, autoantibody-positive, systemic lupus erythematosus (SLE) who are receiving standard therapy (e.g., corticosteroids, antimalarials, immunosuppressives, and nonsteroidal anti-inflammatory drugs), OR
• Active lupus nephritis who are receiving standard therapy (e.g., hydroxychloroquine, cyclophosphamide, corticosteroids with mycophenolate or azathioprine).

Belimumab (Benlysta®) **is considered experimental, investigational, and/or unproven** when used in combination with other biologics for systemic lupus erythematosus or lupus nephritis.

Belimumab (Benlysta®) **is considered experimental, investigational, and/or unproven** for all other non-Food and Drug Administration approved indications, including but not limited to:
• Severe active central nervous system lupus.

Policy Guidelines

None.

Description

Systemic lupus erythematosus (SLE) is an autoimmune disease in which the immune system attacks its own tissues, causing widespread inflammation and tissue damage in the affected organs. The severity of SLE can range from mild to life-threatening. SLE can affect the joint, skin, brain, lungs, kidneys, and blood vessels. People with SLE may experience various symptoms including fatigue, skin rashes, fevers, and pain or swelling in the joints. Other symptoms may include arthritis, lung problems, heart problems, kidney problems, seizures, psychosis, and blood cell and immunological abnormalities. (2, 3) SLE can cause a kidney disease called lupus nephritis. Lupus nephritis is a serious inflammation of the kidneys that can make them stop working. Although there may be no symptoms in the first stages of the disease, as lupus nephritis progresses, swelling, foamy urine, nocturia, and hypertension are commonly seen. (4)

While there is no cure for lupus, medical interventions and lifestyle changes may help manage the disease. (2)

Treatment

The choice of therapy for SLE depends on the predominant symptoms, organ involvement, response to previous therapy, and disease activity and severity. Although treatment is highly individualized, there are some general principles of drug therapy that apply to all patients. In general, all patients with SLE with any degree and type of disease activity should be treated with hydroxychloroquine, unless contraindicated. Additional therapy with corticosteroids, other immunosuppressive agents and nonsteroidal anti-inflammatory drugs is administered based on the severity of disease and the combination of manifestations. (5) In patients with lupus nephritis, the preferred immunosuppressive therapy to induce a renal response may include hydroxychloroquine, cyclophosphamide, corticosteroids with mycophenolate or azathioprine. (6)

Belimumab (Benlysta®)

Belimumab is a monoclonal antibody that affects the actions of the body's immune system and was designed to target B-lymphocyte stimulator (BLyS) protein, which may reduce the number of abnormal B cells thought to be a problem in lupus. Belimumab is used together with other lupus medications to treat active SLE and active lupus nephritis in adults and children at least 5 years of age. (1, 7)

Regulatory Status

- The U.S. Food and Drug Administration (FDA) approved belimumab (Benlysta®) on March 10, 2011, for intravenous (IV) use in adult patients with active, autoantibody-positive lupus (systemic lupus erythematosus) receiving standard therapy, including corticosteroids, antimalarials, immunosuppressives, and nonsteroidal anti-inflammatory drugs.
- Approval of a self-injectable formulation of Benlysta followed on July 21, 2017. Self-administered subcutaneous injection is obtained under the pharmacy benefit and is not addressed in this policy.
- On April 26, 2019, the FDA approved, under priority review, the use of the IV formulation of Benlysta in children with lupus from as young as 5 years of age.
- On December 17, 2020, the FDA extended the current indication to include lupus nephritis in adults. (8)
- On July 27, 2022, the U.S. FDA approved the expanded use of Benlysta for the treatment of children aged 5 to 17 with active lupus nephritis who are receiving standard therapy. (7, 9)
- The current FDA label (May 2024) states Benlysta is indicated for the treatment of patients 5 years of age or older with active systemic lupus erythematosus (SLE) who are receiving standard therapy and for patients 5 years of age or older with active lupus nephritis who are receiving standard therapy. Benlysta is not recommended in patients with severe active central nervous system lupus. (1, 9)

Rationale

This policy is based on the U.S. Food and Drug Administration (FDA) labeled indications for belimumab (Benlysta®).

Clinical Studies
The safety and effectiveness of Benlysta administered intravenously plus standard therapy were evaluated in 4 randomized, double-blind, placebo-controlled trials involving 2,581 adult patients, and one trial involving 93 pediatric patients with systemic lupus erythematosus (SLE) according to the American College of Rheumatology (ACR) criteria. Patients with severe active lupus nephritis and severe active central nervous system (CNS) lupus were excluded. Patients were on a stable standard therapy SLE treatment regimen comprising any of the following (alone or in combination): corticosteroids, antimalarials, nonsteroidal anti-inflammatory drugs (NSAIDs), and immunosuppressives. Use of other biologics and intravenous (IV) cyclophosphamide was not permitted. (1)

In addition, the safety and effectiveness of Benlysta administered IV plus standard therapy was evaluated in a randomized, double-blind, placebo-controlled trial in 448 adult patients with active lupus nephritis. (1)

Clinical Trials Experience with Intravenous Administration in Adults with SLE
Trial 1: SLE - Benlysta 1 mg/kg, 4 mg/kg, 10 mg/kg - Intravenous
Trial 1 (NCT00071487) enrolled 449 patients and evaluated doses of 1, 4, and 10 mg/kg Benlysta plus standard therapy compared with placebo plus standard therapy over 52 weeks in patients with SLE. Patients had to have a Safety of Estrogens in Lupus Erythematosus National Assessment Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) score of >4 at baseline and a history of autoantibodies (anti-nuclear antibody [ANA] and/or anti-double-stranded DNA [anti-dsDNA]), but 28% of the population was autoantibody negative at baseline. The co-primary endpoints were percent change in SELENA-SLEDAI score at Week 24 and time to first flare over 52 weeks. No significant differences between any of the groups receiving Benlysta and the group receiving placebo were observed. Exploratory analysis of this trial identified a subgroup of patients (72%) who were autoantibody positive in whom Benlysta appeared to offer benefit. The results of this trial informed the design of Trials 2 and 3 and led to the selection of a target population and indication that is limited to autoantibody-positive SLE patients. (1)

Trials 2, 3 and 4: SLE - Benlysta 1 mg/kg and 10 mg/kg - Intravenous
Trials 2 (NCT00410384) and 3 (NCT00424476) were randomized, double-blind, placebo-controlled trials in patients with SLE that were similar in design except duration - Trial 2 (N = 819) was 76 weeks' duration and Trial 3 (N = 865) was 52 weeks' duration. Patients had active SLE disease with a SELENA-SLEDAI score ≥6 and positive autoantibody test results at screening. Patients were excluded from the trial if they had ever received treatment with a B-cell-targeted agent or if they were currently receiving other biologic agents. Intravenous cyclophosphamide was not permitted within the previous 6 months or during the trial. Baseline concomitant medications included corticosteroids (Trial 2: 76%, Trial 3: 96%), immunosuppressives (Trial 2:

56%, Trial 3: 42%; including azathioprine, methotrexate, and mycophenolate), and antimalarials (Trial 2: 63%, Trial 3: 67%). Most patients (>70%) were receiving 2 or more classes of SLE medications. (1)

In Trial 2 and Trial 3, 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 (82% in both trials), immune (Trial 2: 74%, Trial 3: 85%), and musculoskeletal (Trial 2: 73%, Trial 3: 59%). Less than 16% of patients had some degree of renal activity and less than 7% of patients had activity in the vascular, cardio-respiratory, or CNS systems.

At screening, patients were stratified by disease severity based on their SELENA-SLEDAI score (≤9 vs. ≥10), proteinuria level (<2 g/24 h vs. ≥2 g/24 h), and race (African or Indigenous-American descent vs. other), and then randomly assigned to receive Benlysta 1 mg/kg, Benlysta 10 mg/kg, or placebo in addition to standard therapy. The patients were administered trial medication intravenously over a 1-hour period on Days 0, 14, 28, and then every 28 days for 48 weeks in Trial 3 and for 72 weeks in Trial 2. The primary efficacy endpoint was a composite endpoint (SLE Responder Index-4 or SRI-4) that defined response as meeting each of the following criteria at Week 52 compared with baseline:

- ≥4-point reduction in the SELENA-SLEDAI score, and
- No new British Isles Lupus Assessment Group (BILAG) A organ domain score or 2 new BILAG B organ domain scores, and
- No worsening (<0.30-point increase) in Physician's Global Assessment (PGA) score. (1)

In both Trials 2 and 3, the proportion of patients with SLE achieving an SRI-4 response, as defined for the primary endpoint, was significantly higher in the group receiving Benlysta 10 mg/kg plus standard therapy than in the group receiving placebo plus standard therapy. The effect on the SRI-4 was not consistently significantly different for patients receiving Benlysta 1 mg/kg plus standard therapy relative to placebo plus standard therapy in both trials. The 1-mg/kg dose is not recommended. The trends in comparisons between the treatment groups for the rates of response for the individual components of the endpoint were generally consistent with that of the SRI-4. At Week 76 in Trial 2, the SRI-4 response rate with Benlysta 10 mg/kg was not significantly different from that of placebo (39% and 32%, respectively). The reduction in disease activity seen in the SRI-4 was related primarily to improvement in the most commonly involved organ systems; namely, mucocutaneous, musculoskeletal, and immune. (1)

Trial 4 was a 2:1 randomized, placebo-controlled trial in Black patients (N = 448) conducted in North America, South America, Europe, and Africa (same study design as Trials 2 and 3 with exceptions of patients having a baseline SELENA-SLEDAI score of >8 and using the modified SLEDAI-2K scoring for proteinuria). The population had a mean age of 39 years (range: 18 to 71) and 97% were female. The proportion of Black patients achieving an SRI-S2K response at Week 52 (primary endpoint), and the individual components of the endpoint, were higher in the group receiving Benlysta 10 mg/kg plus standard therapy relative to the group receiving placebo plus standard therapy. However, the treatment difference was not statistically significant (Table 1). (1)

Table 1. Clinical Response Rate in Patients with SLE after 52 Weeks of Treatment (7)

Response	Trial 2			Trial 3		
	Placebo + Standard Therapy (n=275)	**Benlysta 1 mg/kg + Standard Therapy[a] (n=271)**	**Benlysta 10 mg/kg + Standard Therapy (n=273)**	**Benlysta 10 mg/kg + Standard Therapy (n=287)**	**Benlysta 1 mg/kg + Standard Therapy[a] (n=288)**	**Benlysta 10 mg/kg + Standard Therapy (n=290)**
SLE Responder Index-4 (SRI-4)[b]	34%	41%	43%	44%	51%	58%
Odds ratio (95% CI) vs. placebo		1.3 (0.9, 1.9)	1.5 (1.1, 2.2)		1.6 (1.1, 2.2)	1.8 1.3, 2.6)
Components of SLE Responder Index (SRI-4)						
Percent of patients with reduction in SELENA-SLEDAI-S2K ≥4	36%	43%	47%	46%	53%	58%
Percent of patients with no worsening by BILAG index	65%	75%	69%	73%	79%	81%
Percent of patients with no worsening by PGA	63%	73%	69%	69%	79%	80%

BILAG: British Isles Lupus Assessment Group; CI: Confidence interval; PGA: Physician's Global Assessment; SELENA-SLEDAI: Safety of Estrogens in Lupus Erythematosus National Assessment Systemic Lupus Erythematosus Disease Activity Index; SLE: systemic lupus erythematosus.

[a] The 1-mg/kg dose is not recommended.

[b] Patients dropping out of the trial early or experiencing certain increases in background medication were considered failures in these analyses. A higher proportion of patients receiving placebo were considered failures for this reason compared with the group receiving Benlysta.

The reduction in disease activity seen in the SRI-4 was related primarily to improvement in the most commonly involved organ systems; namely, mucocutaneous, musculoskeletal, and immune.

Effect in Black/African-American Patients: In Trials 2 and 3, exploratory sub-group analyses of SRI-4 response rate in Black patients (n = 148) were performed. The SRI-4 response rate in Black

patients in groups receiving Benlysta plus standard therapy was less than that in the group receiving placebo plus standard therapy (22/50 or 44% for placebo, 15/48 or 31% for Benlysta 1 mg/kg, and 18/50 or 36% for Benlysta 10 mg/kg).

Trial 4 was a 2:1 randomized, placebo-controlled trial in Black patients with SLE (N = 448) conducted in North America, South America, Europe, and Africa (same study design as Trials 2 and 3 with exceptions of patients having a baseline SELENA-SLEDAI score of >8 and using the modified SLEDAI-2K scoring for proteinuria). The population had a mean age of 39 years (range: 18 to 71) and 97% were female. The proportion of Black patients achieving an SRI-S2K response at Week 52 (primary endpoint), and the individual components of the endpoint, were higher in the group receiving Benlysta 10 mg/kg plus standard therapy relative to the group receiving placebo plus standard therapy. However, the treatment difference was not statistically significant (Table 2).

Table 2. Clinical Response Rate in Black Patients with SLE after 52 Weeks of Treatment (Trial 4)

Response[a]	**Placebo + Standard Therapy (n = 149)**	**Benlysta 10 mg/kg + Standard Therapy (n = 298)**
SLE Responder Index (SRI-S2K)[b] Odds Ratio (95% CI)	42%	49% 1.4 (0.9, 2.1) P=0.107
Components of SLE Responder Index (SRI-S2K)		
Percent of patients with reduction in SELENA-SLEDAI-S2K ≥4 Odds Ratio (95% CI)	42%	50% (1.5, 1.0, 2.2)
Percent of patients with no worsening by BILAG Index Odds Ratio (95% CI)	62%	68% 1.2 (0.8, 1.9)
Percent of patients with no worsening by PGA Odds Ratio (95% CI)	64%	70% 1.3 (0.8, 1.9)

CI: Confidence interval; SELENA-SLEDAI: Safety of Estrogens in Lupus Erythematosus National Assessment Systemic Lupus Erythematosus Disease Activity Index; SLE: systemic lupus erythematosus.

[a] Analyses excluded any subject missing a baseline assessment for any of the components (1 for belimumab).

[b] Patients dropping out of the trial early or experiencing certain increases in background medication were considered failures in these analyses. A higher proportion of patients receiving placebo were considered failures for this reason compared with the group receiving Benlysta.

Effect on Concomitant Steroid Treatment: In Trial 2 and Trial 3, 46% and 69% of patients, respectively, were receiving prednisone at doses >7.5 mg/day at baseline. The proportion of patients able to reduce their average prednisone dose by at least 25% to ≤7.5 mg/day during Weeks 40 through 52 was not consistently significantly different for Benlysta plus standard therapy relative to placebo plus standard therapy in both trials. In Trial 2, 17% of patients

receiving Benlysta 10 mg/kg plus standard therapy and 19% of patients receiving Benlysta 1 mg/kg plus standard therapy achieved this level of steroid reduction compared with 13% of patients receiving placebo plus standard therapy. In Trial 3, 19%, 21%, and 12% of patients receiving Benlysta 10 mg/kg, Benlysta 1 mg/kg, and placebo, respectively, plus standard therapy achieved this level of steroid reduction. Effect on Severe SLE Flares: The probability of experiencing a severe SLE flare, as defined by a modification of the SELENA Trial flare criteria, which excluded severe flares triggered only by an increase of the SELENA-SLEDAI score to >12, was calculated for both Trials 2 and 3. The proportion of patients having at least 1 severe flare over 52 weeks was not consistently significantly different for Benlysta plus standard therapy relative to placebo plus standard therapy in both trials. In Trial 2, 18% of patients receiving Benlysta 10 mg/kg plus standard therapy and 16% of patients receiving Benlysta 1 mg/kg plus standard therapy had a severe flare compared with 24% of patients receiving placebo plus standard therapy. In Trial 3, 14%, 18%, and 23% of patients receiving Benlysta 10 mg/kg, Benlysta 1 mg/kg and placebo, respectively, plus standard therapy had a severe flare.

Clinical Trials with Intravenous Administration in Adults with Lupus Nephritis

Trial 5: Lupus Nephritis – Benlysta 10 mg/kg - Intravenous

The safety and effectiveness of Benlysta 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 patients with active proliferative and/or membranous lupus nephritis (Trial 5). 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); the majority (88%) were female. (1)

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 m^2 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 <0.5 g/g and eGFR and ≥90 mL/min/1.73m^2 or no decrease in eGFR of >10% from pre-flare value.
- PERR at Week 52.
- 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). (1)

The proportion of patients achieving PERR at Week 104 was significantly higher in patients receiving Benlysta plus standard therapy compared with placebo plus standard therapy. The major secondary endpoints also showed significant improvement with Benlysta plus standard therapy compared with placebo plus standard therapy. (1)

Clinical Trials with Intravenous Administration in Pediatric Patients with SLE

Trial 6: Benlysta 10 mg/kg in Pediatric Patients - Intravenous

The safety and efficacy of Benlysta 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 ACR 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 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). (1)

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 Benlysta plus standard therapy compared with placebo plus standard therapy (Table 3). (1)

Table 3. Pediatric Response Rate at Week 52[a] (Trial 6) (1)

Response[b]	**Placebo + Standard Therapy (n = 39)**	**Benlysta 10 mg/kg + Standard Therapy (n = 53)**
SLE Responder Index	44%	53%
Odds Ratio (95% CI) vs. Placebo		1.49 (0.64, 3.46)
Components of SLE Responder Index		
Percent of patients with reduction in SELENA-SLEDAI ≥4	44%	55%
Percent of patients with no worsening by BILAG index	62%	74%
Percent of patients with no worsening by PGA	67%	76%
Other endpoints		

SRI-6 using SELENA-SLEDAI ≥6-point reduction	34%	41%
Proportion of patients with a sustained SRI response	41%	43%

BILAG: British Isles Lupus Assessment Group; CI: confidence interval; PGA: Physician's Global Assessment; SELENA-SLEDAI: Safety of Estrogens in Lupus Erythematosus National Assessment Systemic Lupus Erythematosus Disease Activity Index; SLE: systemic lupus erythematosus.

[a] Based on a non-powered trial.

[b] Analyses excluded any subject missing a baseline assessment for any of the components (1 for placebo).

Effect on Concomitant Steroid Treatment: At baseline, 95% of pediatric patients were receiving prednisone. Among those pediatric patients, 20% of pediatric patients receiving Benlysta plus standard therapy reduced their average prednisone dose by at least 25% per day during Weeks 44 through 52 compared with 21% of pediatric patients on placebo plus standard therapy.

Effect on Severe SLE Flares: In Trial 6, 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 analyzed. The proportion of pediatric patients reporting at least one severe flare during the study was numerically lower in pediatric patients receiving Benlysta plus standard therapy (17%) compared with those receiving placebo plus standard therapy (35%). Pediatric patients receiving Benlysta 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 Benlysta plus standard therapy compared with 113 days in pediatric patients receiving placebo plus standard therapy.

Use of Benlysta in Patients with Severe Active Central Nervous System Lupus and/or Use in Combination with Other Biologics

Per the FDA label, the efficacy of Benlysta has not been established in patients with severe active central nervous system lupus. Also, Benlysta has not been studied and is not recommended with other biologic therapies for SLE or lupus nephritis. (1) Therefore, use of belimumab in these situations is considered experimental, investigational and/or unproven.

Summary of Evidence

Based on the clinical studies provided to the U.S. Food and Drug Administration (FDA), belimumab (Benlysta®) may be considered medically necessary for the treatment of patients aged 5 years and older with active, autoantibody-positive systemic lupus erythematosus (SLE) who are receiving standard therapy (e.g., corticosteroids, antimalarials, immunosuppressives, and nonsteroidal anti-inflammatory drugs) and in patients aged 5 years and older with active lupus nephritis who are receiving standard therapy (e.g., hydroxychloroquine, cyclophosphamide, corticosteroids with mycophenolate or azathioprine).

Per the U.S. FDA label, the efficacy of belimumab (Benlysta) has not been established in individuals with severe active central nervous system lupus. Belimumab (Benlysta) is not recommended in combination with other biologic therapies for individuals with systemic lupus erythematosus or lupus nephritis.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	None
HCPCS Codes	J0490

*Current Procedural Terminology (CPT®) ©2024 American Medical Association: Chicago, IL.

References

U.S. Food and Drug Administration Label:

1. FDA Highlights of Prescribing Information: Benlysta. May 2024. Available at: <https://www.accessdata.fda.gov> (accessed June 17, 2025).

Other:

2. Center for Disease Control and Prevention. Lupus Basics (SLE). May 15, 2024. Available at: <https://www.cdc.gov> (accessed June 17, 2025).
3. Center for Disease Control and Prevention. Symptoms of Lupus. May 15, 2024. Available at: <https://www.cdc.gov> (accessed June 17, 2025).
4. Lupus Foundation of America. Lupus and the kidneys. January 13, 2021. Available at: <https://www.lupus.org> (accessed June 17, 2025).
5. Wallace Daniel J. Systemic lupus erythematosus in adults: Overview of the management and prognosis. In: UpToDate, Pisetsky D, Rigby W (Eds), UpToDate, Waltham, MA. Available at: <https://www.uptodate.com> (accessed June 17, 2025).
6. Falk RJ, Dall'Era M, Appel GB. Lupus nephritis: Initial and subsequent therapy for focal or diffuse lupus nephritis. In: UpToDate, Pisetsky D, Rigby W. (Eds), UpToDate, Waltham, MA. Available at: <https://www.uptodate.com> (accessed June 17, 2025).
7. Benlysta. 2024. Available at: <https://www.drugs.com> (accessed June 17, 2025).
8. Benlysta FDA approval history. May 2024. Available at: <https://www.drugs.com> (accessed June 17, 2025).
9. GSK (GlaxoSmithKline) announces US FDA approval of Benlysta (belimumab) for pediatric patients with active lupus nephritis. July 2022. Available at: <https://www.drugs.com>

(accessed June 17, 2025).

Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
08/15/2025	Document updated with literature review. Separated exclusionary versus non-FDA approved conditions in the experimental, investigational and/or unproven statements. Added "non-Food and Drug Administration" to the experimental, investigational and/or unproven statement for severe active central nervous system lupus. Added references 3 and 8; One reference was removed.
04/01/2025	Document updated with literature review. The following changes were made in Coverage: 1) Added "hydroxychloroquine" and "azathioprine" as additional examples of standard therapy for active lupus nephritis 2) Expanded the experimental, investigational, and/or unproven statement to include "for systemic lupus erythematosus or lupus nephritis" when used in combination with other biologics. Added reference 5, others updated.
03/15/2024	Reviewed. No changes.
03/15/2023	Document updated with literature review. The following changes were made to Coverage: 1) Added NOTE 1: This policy is specific to Belimumab (Benlysta) intravenous use. Self-administered subcutaneous injection is obtained under the pharmacy benefit. 2) Expanded coverage from "adult" patients to "patients for 5 years of age or older" with active lupus nephritis who are receiving standard therapy. Added reference 7; others updated.
07/01/2022	Reviewed. No changes.
05/15/2021	Document updated with literature review. The following changes were made to Coverage: 1) Added conditional coverage for lupus nephritis; and 2) Removed "severe active lupus nephritis" from list of contraindications and moved remaining list of contraindications to experimental, investigational and/or unproven statement. Added/updated the following references: 2, 4 and 6.

10/01/2020	New medical document originating from RX501.051. Belimumab (Benlysta®) may be considered medically necessary for the treatment of patients aged 5 years and older with active, autoantibody-positive, systemic lupus erythematosus (SLE) who are receiving standard therapy (e.g., corticosteroids, antimalarials, immunosuppressives, and nonsteroidal anti-inflammatory drugs). Belimumab (Benlysta®) is contraindicated for patients with the following: 1) Severe active lupus nephritis, 2) Severe active central nervous system lupus, or 3) Those taking other biologics or intravenous cyclophosphamide. Belimumab (Benlysta®) is considered experimental, investigational and/or unproven for all other indications.