Benlysta® (belimumab)

Innoustrations for Use
This Drug Policy provides assistance in interpreting UnitedHealthcare benefit plans. When deciding coverage, the enrollee specific document must be referenced. The terms of an enrollee’s document (e.g., Certificate of Coverage (COC) or Summary Plan Description (SPD)) may differ greatly. In the event of a conflict, the enrollee’s specific benefit document supersedes this Drug Policy. All reviewers must first identify enrollee eligibility, any federal or state regulatory requirements, and the plan benefit coverage prior to use of this Drug Policy. Other Policies and Coverage Determination Guidelines may apply. UnitedHealthcare reserves the right, in its sole discretion, to modify its Policies and Guidelines as necessary. This 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 MCG™ Care Guidelines, to assist us in administering health benefits. The MCG™ Care Guidelines 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.

Coverage Rationale
Belimumab (Benlysta®) is proven for adults with active systemic lupus erythematosus (SLE) who meet both of the following criteria:
1) Autoantibody positive [e.g., anti-nuclear antibody (ANA) titer ≥ 1:80 or anti-dsDNA level ≥ 30 IU/mL] \(^1,3,5\) -AND- 
2) Currently receiving at least one standard of care treatment for active systemic lupus erythematosus (e.g., antimalarials, corticosteroids, or immunosuppressants) \(^1,7\)

Additional information to support medical necessity review where applicable:
The above indications and criteria also apply to medical necessity review.
Belimumab is **unproven and not medically necessary** for:
1) Severe active lupus nephritis
2) Severe active central nervous system lupus
3) Use in combination with other biologics or intravenous cyclophosphamide
4) Waldenström macroglobulinemia
5) Sjögren's syndrome
6) Rheumatoid arthritis

Medicare does not have a National Coverage Determination (NCD) for Benlysta (belimumab). Local Coverage Determinations (LCDs) do not exist at this time. However, HCPC Code J0490 Benlysta (belimumab) is addressed in the Articles for Approved Drugs and Biologicals: Includes Cancer Chemotherapeutic Agents.

Medicare covers outpatient (Part B) drugs that are furnished "incident to" a physician's service provided that the drugs are not usually self-administered by the patients who take them. See the Medicare Benefit Policy Manual (Pub. 100-2), Chapter 15, §50 Drugs and Biologicals at http://www.cms.hhs.gov/manuals/Downloads/bp102c15.pdf. (Accessed April 3, 2014)

**BENEFIT CONSIDERATIONS**

Some Certificates of Coverage allow coverage of experimental/investigational/unproven treatments for life-threatening illnesses when certain conditions are met. The enrollee-specific benefit 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. See the Policy and Procedure addressing the treatment of serious rare diseases.

**CLINICAL EVIDENCE**

**Proven Systemic Lupus Erythematosus:**
Ginzler et al evaluated the efficacy/safety of belimumab plus standard therapy in patients (n=449) with active systemic lupus erythematosus (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 SELENA SLEDAI, frequency of 1 new BILAG A or 2 new B scores, frequencies of mild-moderate and severe flares as defined by SFI, and change in corticosteroid use. Total belimumab exposure over 7 years (double-blind 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.

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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, the 1-year effects of belimumab treatment on organ domain-specific systemic lupus erythematosus (SLE) disease activity demonstrated significant improvements from baseline in patients treated with belimumab 1 mg/kg and 10 mg/kg on the musculoskeletal domain (61.2% [p < 0.01] and 60.2% [p < 0.05] vs 50%) and mucocutaneous domain (47.9% [p < 0.05] and 47.6% [p < 0.05] vs 39.1%) evaluated by the BILAG domain scores. In an assessment using the SELENA-SLEDAI, significant improvements in the belimumab-treated patients occurred in the mucocutaneous (10 mg/kg, p < 0.01), musculoskeletal (1 mg/kg, p < 0.05), immunological (1 and 10 mg/kg, p < 0.001), vascular (10 mg/kg, p < 0.05), and CNS (1 mg/kg, p < 0.05; 10 mg/kg, p < 0.01) domains. Researchers concluded that treatment with belimumab improved overall SLE disease activity in the most common musculoskeletal and mucocutaneous organ domains. Additionally, less worsening occurred in the haematological, immunological and renal domains.

In a phase III, multicenter, randomized, placebo-controlled, phase III trial, researchers evaluated the efficacy and safety of belimumab in combination with standard therapy in patients with active systemic lupus erythematosus (SLE) over 76 weeks (BLISS-76). Patients (aged ≥18 years) who met the American College of Rheumatology criteria for systemic lupus erythematosus and had active disease (score ≥6 at screening on SELENA-SLEDAI) were eligible for enrolment. Other inclusion criteria were two positive ANA (titre ≥1:80) or anti-dsDNA antibody (≥30 IU/mL) test results, and a stable treatment regimen for ≥30 days before first study dose with prednisone (or equivalent) alone (7.5–40 mg/day) or combined (0–40 mg/day) with antimalarial drugs, nonsteroidal anti-inflammatory drugs, and/or immunosuppressive therapies. Patients were excluded for serious inter-current illness, severe active lupus nephritis, severe central nervous system manifestations, and pregnancy. Additional medication exclusions included intravenous (IV) cyclophosphamide within 6 months of screening; a tumor necrosis factor inhibitor, anakinra, IV immune globulin, prednisone >100 mg/day, or plasmapheresis within 3 months of screening; and immunization with a live vaccine within 1 month of screening. Patients were randomized to receive 1 mg/kg belimumab (n=271), 10 mg/kg belimumab (n=273), or placebo (n=275) IV on days 0, 14, and 28 and then every 28 days for 72 weeks. The primary efficacy endpoint was the SLE Responder Index (SRI) response rate at week 52 (an SRI response was defined as a ≥4-point reduction in SELENA-SLEDAI score, no new British Isles Lupus Assessment Group [BILAG] A organ domain score and no more than 1 new BILAG B score, and no worsening in physician's global assessment score versus baseline). Secondary end points included SRI response rate at week 76, percentage of patients with a ≥4-point reduction from baseline in SELENA–SLEDAI score at week 52, change in physician's global assessment score at week 24, change in Short Form 36 version 2 (SF-36v2) health survey physical component summary (PCS) score at week 24, and percentage of patients with a mean prednisone dose that was decreased ≥25% from baseline and was ≤7.5 mg/day during weeks 40–52. Belimumab at 10 mg/kg plus standard therapy met the primary efficacy end point, generating a significantly greater SRI response at week 52 compared with placebo (43.2% versus 33.5%; p=0.017). The rate with 1 mg/kg belimumab was 40.6% (p=0.089). Though not statistically significant, the SRI response rates at week 76 (secondary endpoint) were 32.4%, 39.1% (p=0.11), and 38.5% (p=0.13) with placebo, 1 mg/kg belimumab, and 10 mg/kg belimumab, respectively. Further post hoc sensitivity analyses evaluating higher SELENA–SLEDAI score thresholds, 10 mg/kg belimumab achieved better discrimination at weeks 52 and 76. Risk of severe flares over 76 weeks (based on the modified SLE Flare Index) was reduced with 1 mg/kg belimumab (34%) (p=0.023) and 10 mg/kg belimumab (23%) (p=0.13). Serious and severe adverse events, including infections, laboratory abnormalities, malignancies, and deaths, were comparable across all groups. Researchers conclude that Belimumab in combination with standard therapy significantly improved SRI.
response rate, reduced SLE disease activity and severe flares, and was generally well tolerated in SLE until 76 weeks.

Navarra et al evaluated the efficacy and safety of belimumab with standard of care (SOC) in patients with seropositive systemic lupus erythematosus (SLE) in a phase III, randomized, placebo-controlled, multicentre, 52-week trial (BLISS-52). Patients (aged ≥18 years) who met the American College of Rheumatology criteria for systemic lupus erythematosus and had active disease (score ≥6 at screening on SELENA-SLEDAI) were eligible for enrolment. Other inclusion criteria were unequivocally positive ANA (titre ≥1:80) or anti-dsDNA antibody (≥30 IU/mL), and a stable treatment regimen with fixed doses of prednisone (0–40 mg/day), or non-steroidal anti-inflammatory, antimalarial, or immunosuppressive drugs for at least 30 days before the first study dose. The main exclusion criteria were severe active lupus nephritis or CNS lupus; pregnancy; and previous treatment with any B-lymphocyte-targeted drug (including rituximab), intravenous cyclophosphamide within 6 months of enrolment, and intravenous immune globulin or prednisone (>100 mg/day) within 3 months. Patients were randomly assigned to belimumab 1 mg/kg (n=289) or 10 mg/kg (n=290), or placebo (n=288) in addition to SOC. Primary efficacy endpoint was improvement in the Systemic Lupus Erythematosus Responder Index (SRI) at week 52 (reduction ≥4 points in SELENA-SLEDAI score; no new British Isles Lupus Assessment Group [BILAG] A organ domain score and no more than 1 new B organ domain score; and no worsening [<0.3 increase] in Physician’s Global Assessment [PGA] score) versus baseline. Secondary endpoints included proportion of patients with at least a 4-point reduction from baseline in SELENA-SLEDAI score at week 52, mean change in PGA score at week 24, mean change in SF-36 physical component summary score at week 24, and proportion of patients with an average reduction in prednisone dose of at least 25% from baseline to 7.5 mg/day or less during weeks 40 to 52. Significantly higher SRI rates were noted with belimumab 1 mg/kg (148 [51%], odds ratio 1.55 [95% CI 1.10-2.19]; p=0.0129) and 10 mg/kg (167 [58%], 1.83 [1.30-2.59]; p=0.0006) than with placebo (125 [44%]) at week 52. More patients had their SELENA-SLEDAI score reduced by at least 4 points during 52 weeks with belimumab 1 mg/kg (153 [53%], 1.51 [1.07-2.14]; p=0.0189) and 10 mg/kg (169 [58%], 1.71 [1.21-2.41]; p=0.0024) than with placebo (132 [46%]). More patients given belimumab 1 mg/kg (226 [78%], 1.38 [0.93-2.04]; p=0.1064) and 10 mg/kg (236 [81%], 1.62 [1.09-2.42]; p=0.0181) had no new BILAG A or no more than 1 new B flare than did those in the placebo group (210 [73%]). No worsening in PGA score was noted in more patients with belimumab 1 mg/kg (227 [79%], 1.68 [1.15-2.47]; p=0.0078) and 10 mg/kg (231 [80%], 1.74 [1.18-2.55]; p=0.0048) than with placebo (199 [69%]). Rates of adverse events were similar in the groups given belimumab 1 mg/kg and 10 mg/kg, and placebo: serious infection was reported in 22 (8%), 13 (4%), and 17 (6%) patients, respectively, and severe or serious hypersensitivity reactions on an infusion day were reported in two (<1%), two (<1%), and no patients, respectively. No malignant diseases were reported. Researchers conclude that use of belimumab in controlling SLE in a broad range of patients is a safe and efficacious management option.

Unproven
Efficacy of belimumab has not been established in patients with severe active lupus nephritis or severe active CNS lupus, and belimumab has not been studied in combination with other biologic agents or IV cyclophosphamide. Therefore, use of belimumab in these situations is unproven.

The use of belimumab is also being investigated for treatment of other conditions, such as, 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.

Professional Societies
American College of Rheumatology (ACR)
In 2011, the ACR released a Hotline in regards to use of belimumab in systemic lupus erythematosus (SLE). Their findings are as follows.8
Belimumab is the first new medication approved by the USA FDA for SLE in over 50 years.
The patients most appropriate for therapy may be seropositive SLE patients with active musculoskeletal, cutaneous, and immunological activity despite standard of care.
Belimumab has not been studied in severe active lupus nephritis or severe active CNS lupus.
Belimumab was not associated with an increase in serious adverse events, infections or malignancy during clinical trials. Severe hypersensitivity reactions, though rare, were reported in belimumab treated patients.
Longer term follow-up of larger numbers of diverse SLE patients is needed to better assess this agent’s safety.

In 1999, the ACR ad hoc committee developed standard of care guidelines for the management of SLE. The following are the ACR treatment recommendations from the Guidelines for Referral and Management of Systemic Lupus Erythematosus in Adults:

**Treatment of Mild SLE**
- **Topical Sunscreens:** Patients with SLE may experience cutaneous or systemic disease flares when exposed to ultraviolet light; these patients should be encouraged to protect themselves from such exposure. Wearing protective clothing, applying sunscreens with a sun protection factor of at least 15 whenever outdoors and avoidance of sunbathing should be emphasized.
- **Topical glucocorticoid preparations:** Creams, ointments, and other vehicles are used to apply glucocorticoids to affected areas. Intermediate- rather than high-strength topical steroids should be used on steroid-sensitive areas that are prone to atrophy, such as the face. Cyclical application of more potent glucocorticoids may be required.
- **NSAIDs:** NSAIDs are sometimes helpful for control of fever, arthritis, and mild serositis. However, salicylate-induced hepatitis has been noted among patients with SLE, and aseptic meningitis has developed in SLE patients given ibuprofen. Other NSAIDs may cause similar reactions. NSAIDs may cause or aggravate hypertension, peripheral edema, and renal impairment in SLE patients. Whether the COX-2 inhibitors will have a better safety profile among patients with SLE remains unknown.
- **Antimalarial agents (e.g., hydroxychloroquine):** Antimalarial agents are useful for skin and joint manifestations of SLE, for preventing flares, and for other constitutional symptoms of the disease. They may also reduce fatigue and decrease levels of low-density lipoproteins.
- **Oral glucocorticoids:** Patients with mild SLE usually do not need systemic glucocorticoid treatment. However, some patients do not have an acceptable quality of life unless treated with low-dose daily or alternate-day glucocorticoids (≤ 10 mg of prednisone/day or equivalent). Given the significant toxicity of glucocorticoids, initiation of therapy with these agents, along with strategies to minimize steroid side effects (e.g., consideration of steroid-sparing agents, and prevention of osteoporosis and infections), is an indication for referral.

**Treatment of serious, life-threatening, or organ-threatening SLE**
- **High-dose glucocorticoids:** Glucocorticoids are used for refractory manifestations of SLE, as well as for severe organ-threatening disease. High-dose, daily glucocorticoid therapy (40–60 mg/day of prednisone) improves survival among patients with severe forms of SLE nephritis, but is associated with virtually universal undesirable side effects. The dosage and mode of administration of glucocorticoids will depend on the nature and severity of the condition. Thus, refractory serositis may require relatively low doses, up to 20 mg per day of prednisone or equivalent. However, depending on the individual’s sensitivity to steroids, that dosage may cause significant side effects. The treatment of active SLE nephritis, cerebritis, or thrombocytopenia may require high doses of 40–60 mg of prednisone per day, or intravenous pulses of up to 1 gm of methylprednisolone per day for 3 consecutive days. Studies of monthly high-dose intravenous methylprednisolone (in addition to daily oral glucocorticoids) have shown a positive effect on severe SLE nephritis, although the therapy is not as effective as intermittent intravenous cyclophosphamide added to oral glucocorticoids. The exact
dosage will depend on the sensitivity of the individual, and the exact nature of his or her disease.

- **Immunosuppressive/cytotoxic agents:** A number of immunosuppressive/cytotoxic medications have been used to treat SLE. These include azathioprine, cyclophosphamide, methotrexate, chlorambucil, cyclosporine, and nitrogen mustard. The choice of drug will depend on the nature and severity of the condition, as well as individual preference. For example, for patients with particularly severe arthritis, methotrexate may be preferred as the first cytotoxic medication, whereas for SLE nephritis, azathioprine or cyclophosphamide may be chosen first. In a series of long-term studies (> 20 years of follow-up) in patients with SLE nephritis, treatment with glucocorticoids plus cyclophosphamide for > 2 years appears to be superior to glucocorticoids plus azathioprine, and both seem superior to glucocorticoids alone in preventing renal failure in these patients. There is evidence that cytotoxic agents plus low-dose steroids prevent scarring in the kidney better than do glucocorticoids alone. However, some patients with severe disease (renal or extrarenal) respond well over both the short term and the long term to glucocorticoids alone, or they require only a few months of treatment with cytotoxic agents plus glucocorticoids to achieve long-term improvement. Nonrenal manifestations of SLE that may respond to cytotoxic drugs if glucocorticoid treatment is unsuccessful or is not tolerated include cytopenia, CNS manifestations, pulmonary hemorrhage, and vasculitis. There are several reports of SLE arthritis or nephritis responding to methotrexate. Variations in responses to therapy, in addition to the considerable toxicity of all of the regimens, necessitate expert management.

- **Management of severe SLE without renal involvement:** Additional treatment approaches have been used in certain circumstances among patients with SLE. In a controlled trial, intravenous gamma globulin was not superior to daily high-dose glucocorticoid therapy among patients with idiopathic thrombocytopenic purpura. However, intravenous gamma globulin can produce short-term improvement in patients with SLE-related immune thrombocytopenia or hemolytic anemia, as can splenectomy, danazol, cyclosporine, and various chemotherapy regimens. Plasmapheresis has not provided added benefit to glucocorticoids plus cyclophosphamide in controlled trials of SLE nephritis. However, apheresis has been used for cytopenias, cryoglobulinemia, and occasionally for CNS disease. Plasmapheresis or plasma exchange is often lifesaving in SLE-associated thrombotic thrombocytopenic purpura. Cyclosporin A has been used to treat severe disease; however, its low efficacy-to-toxicity ratio requires that it be administered by a physician who is expert in its use. Dapsone has been used primarily for refractory skin lesions. Retinoid derivatives have also been used for resistant skin lesions. Patients who have had thrombotic events in the setting of SLE usually require anticoagulation rather than immunosuppression.

- **End-stage renal disease:** In spite of optimal therapy, in some cases SLE advances to end-stage renal disease, necessitating dialysis and/or renal transplantation. The rate of recurrence of SLE in transplanted kidneys is ~6%, and rejection rates may be somewhat higher than those in the general population of patients who have undergone renal transplantation. However, most patients do well, and choosing this modality rather than vigorous immunosuppressive treatment should be considered by both patient and physician.

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**U.S. FOOD AND DRUG ADMINISTRATION (FDA)**

Benlysta (belimumab) is a B-lymphocyte stimulator (BLyS)-specific inhibitor FDA-labeled for the treatment of adult patients with active, autoantibody-positive, systemic lupus erythematosus who are receiving standard therapy.1

Limitations of Use:1

- The efficacy of Benlysta has not been evaluated in patients with severe active lupus nephritis or severe active central nervous system lupus.

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• Benlysta has not been studied in combination with other biologics or intravenous cyclophosphamide.

Use of Benlysta is not recommended in these situations.

The safety and efficacy of Benlysta has not been established in children.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

**APPLICABLE CODES**

The [Current Procedural Terminology (CPT), HCPCS and/or ICD-9] codes listed in this policy are for reference purposes only. Listing of a service or device code in this policy does not imply that the service described by this code is a covered or non-covered health service. Coverage is determined by the benefit document.

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**ICD-10 Codes (Preview Draft)**

In preparation for the transition from ICD-9 to ICD-10 medical coding on October 1, 2015*, a sample listing of the ICD-10 CM and/or ICD-10 PCS codes associated with this policy has been provided below for your reference. This list of codes may not be all inclusive and will be updated to reflect any applicable revisions to the ICD-10 code set and/or clinical guidelines outlined in this policy. *The effective date for ICD-10 code set implementation is subject to change.

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**REFERENCES**


2. FDA Briefing Document for the Arthritis Advisory Committee Meeting: Benlysta/Belimumab. November 16, 2010. Available at:

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**POLICY HISTORY/REVISION INFORMATION**

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