BENLYSTA® (BELIMUMAB)

Policy Number: 2019D0046I **Effective Date**: March 1, 2019

Instructions for Use

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Related Commercial Policy

- Provider Administered Drugs – Site of Care Review Guidelines

COVERAGE RATIONALE

See Benefit Considerations

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

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

I. Diagnosis of active systemic lupus erythematosis; **and**
II. **One** of the following:
   A. Anti-nuclear antibody (ANA) titer ≥ 1:80
   B. Anti-double-stranded DNA (anti-dsDNA) level ≥ 30 IU/mL][1,3-5]
   and
III. Currently receiving at least **one** standard of care treatment for active systemic lupus erythematosus (e.g., antimalarials, corticosteroids, or immunosuppressants)[1-7,10]; **and**
IV. Benlysta is initiated and titrated according to US Food and Drug Administration labeled dosing for SLE up to a maximum of 10mg/kg every 4 weeks.[1]

Benlysta is unproven and not medically necessary for:

- Severe active lupus nephritis[1]
- Severe active central nervous system (CNS) lupus[1]
- Use in combination with other biologics or intravenous cyclophosphamide[1]
- Waldenström macroglobulinemia
- Sjögren's syndrome
- Rheumatoid arthritis

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

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

Limitations of Use[1]

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

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 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]

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.

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 Coverage Determination Guidelines may apply.

HCPCS Code	Description
J0490	Injection, belimumab, 10 mg

ICD-10 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

BENEFIT CONSIDERATIONS

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

CLINICAL EVIDENCE

Proven

Systemic Lupus Erythematosus

Belimumab is indicated for the treatment of active, autoantibody-positive, systemic lupus erythematosus (SLE) who are receiving standard therapy.[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 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[14]) 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).[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 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.

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.[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, 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

The European League Against Rheumatism (EULAR)

In 2008, EULAR published their recommendations for the treatment of systemic lupus erythematosus (SLE). Their recommendations are as follows.[18]

General Management

Treatment

In the treatment of SLE without major organ manifestations antimalarials and/or glucocorticoids are of benefit and may be used. NSAIDs may be used judiciously for limited periods of time at patients at low risk for their complications. In non-responsive patients or patients not being able to reduce steroids below doses acceptable for chronic use, immunosuppressive agents such as azathioprine, mycophenolate mofetil, and methotrexate should also be considered.

Adjunct Therapy

Photo-protection may be beneficial in patients with skin manifestations and should be considered. Lifestyle modifications (smoking cessation, weight control, exercise) are likely to be beneficial for patient outcomes and should be encouraged. Depending on the individual medication and the clinical situation, other agents (low-dose aspirin, calcium/vitamin D, biphosphonates, statins, anti-hypertensives (including angiotensin converting enzyme inhibitors)) should be considered. Estrogens (oral contraceptives, hormonal replacement therapy) may be used but accompanying risks should be assessed.

Neuropsychiatric Lupus

More expansive EULAR guidelines for neuropsychiatric lupus were published in 2010.[19] Treatment guidelines from 2008 are below:

Treatment

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

Pregnancy In Lupus

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

Mother

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

Fetus

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

Anti-Phospholipid Syndrome

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

SLE and anti-phospholipid syndrome combined unfractionated or LMW heparin and aspirin reduce pregnancy loss and thrombosis and should be considered.

Lupus Nephritis

More expansive EULAR guidelines for lupus nephritis were published in 2012.[20]
Treatment guidelines from 2008 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.

CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

Medicare does not have a National Coverage Determination (NCD) for BENLYSTA® (belimumab). Local Coverage Determinations (LCDs) exist; refer to the LCDs for Drugs and Biologics (Non-chemotherapy).

Medicare may cover 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, Chapter 15, §50 Drugs and Biologicals.
(Accessed March 6, 2018)

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POLICY HISTORY/REVISION INFORMATION

Date	Action/Description
04/01/2019	Updated list of related policies to reflect title change for *Provider Administered Drugs – Site of Care Review Guideline* (previously titled *Specialty Medication Administration – Site of Care Review Guidelines*)
03/01/2019	Reorganized policy template; simplified and relocated *Instructions for Use* and *Benefit Considerations* section. Archived previous policy version 2018D0046H.
07/01/2018	Added reference link to the policy titled *Specialty Medication Administration – Site of Care Review Guidelines*
05/01/2018	Annual review. Added language about IV vs. subcutaneous formulations. Approved by the National Pharmacy and Therapeutics Committee 04/18/2018. Updated CMS statement and references. Policy 2017D0046G archived.
07/01/2017	Annual review. Updated coverage rationale to include diagnosis and dosing criteria. Transferred to new policy template. Added background and references. Updated CMS statement. Removed ICD-9 codes. Approved by the National Pharmacy and Therapeutics Committee 04/26/2017. Policy 2016D0046F archived.
07/01/2016	Annual review. Minor formatting changes to coverage rationale with no changes to clinical intent. Updated CMS statement, clinical evidence and references. Approved by the National Pharmacy and Therapeutics Committee 05/20/2016. Policy 2015D0046E archived.
10/01/2015	Updated Applicable Codes for ICD-10 transition. Policy 2015D0046D archived.

Date	Action/Description
08/01/2015	Annual review. No changes to Coverage Rationale. Updated CMS, Clinical Evidence, U.S. FDA, and references. Approved by the National Pharmacy and Therapeutics Committee 05/20/2015. Policy 2014D0046C archived.
08/01/2014	Annual review. Updated CMS, Clinical Evidence, U.S. FDA, and References. Approved by the National Pharmacy and Therapeutics Committee 05/21/2014. Policy 2013D0046B archived.
07/01/2013	Policy revised per annual review. Removed age 18 requirement from Coverage Rationale. Updated Benefits Considerations and References. Approved by the National Pharmacy and Therapeutics Committee 05/21/2013. Policy 2012D0046A archived.
11/14/2012	New policy 2012D0046A. Approved by the National Pharmacy and Therapeutics Committee 05/15/2012.

INSTRUCTIONS FOR USE

This Medical Benefit Drug Policy provides assistance in interpreting UnitedHealthcare 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 benefit 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 MCG™ Care Guidelines, 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.