belimumab (Benlysta®)

Policy # 00295
Original Effective Date: 04/13/2011
Current Effective Date: 05/16/2018

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider the use of belimumab (Benlysta®)‡ for the treatment of systemic lupus erythematosus (SLE) in adult patients who are receiving standard therapy to be **eligible for coverage**.

Patient Selection Criteria
Coverage eligibility for the use of belimumab (Benlysta) will be considered when all of the following patient selection criteria are met:

- Patient is ≥ 18 years of age; and
- Patient has diagnosis of active SLE; and
- Patient is autoantibody-positive (ANA [anti-nuclear antibody] or anti- double-stranded deoxyribonucleic acid [anti-dsDNA]); and
- Patient is receiving standard therapy (corticosteroids, antimalarials, non-steroidal anti-inflammatory drugs [NSAIDs], immunosuppressives); and
- Patient is NOT receiving other biologics or intravenous (IV) cyclophosphamide.

When Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of belimumab (Benlysta) when patient selection criteria are not met OR for use in any other indication (including, but not limited to severe active lupus nephritis or severe active central nervous system [CNS] lupus) not listed in the above patient selection criteria to be **investigational.***

Background/Overview

Benlysta is a new molecular entity that targets a novel pathway for the treatment of SLE. Benlysta is a recombinant, fully human, IgG1λ monoclonal antibody that binds and inhibits the biological activity of soluble B lymphocyte stimulator (BLyS), protein. BLyS is a member of the tumor necrosis factor (TNF) ligand family and is also known as B-cell activating factor belonging to the TNF family (BAFF). It plays a role in B cell selection and survival and is expressed by a variety of cell types, including neutrophils, monocytes, macrophages, dendritic cells, and T cells. There are 3 receptors for BLyS. BLyS receptor 3 (BR3) is the

only BLyS receptor found on newly formed and mature primary B cells, and BLyS is its only ligand. Blockade by Benlysta is expected to affect these cells more than memory B cells and plasma cells, which have other ligand activators.

Benlysta is available in two forms: IV and subcutaneous. The IV form is dosed at 10 mg/kg at 2 week intervals for the first 3 doses and at 4 week intervals thereafter. The subcutaneous version is given 200 mg once weekly.

Systemic Lupus Erythematosus
SLE is a chronic inflammatory disease of unknown cause that can affect the mucocutaneous, gastrointestinal, hematologic, musculoskeletal, neurologic, psychiatric, pulmonary, renal, and reproductive systems. Immunologic abnormalities are a prominent feature of the disease. For example, autoantibodies against dsDNA (i.e. anti-dsDNA) and Smith nuclear antigen (i.e. anti-Sm) are highly specific for SLE. Increases in anti-dsDNA titers, erythrocyte sedimentation rate (ESR), and serum C-reactive protein (CRP), and a decrease in serum complement levels, often precede active SLE.

Treatment options for SLE include: prednisone, hydroxychloroquine, NSAIDs and immunosuppressive agents, such as cyclophosphamide, methotrexate, azathioprine, and mycophenolate.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
In March 2011, the FDA approved belimumab (Benlysta) to treat patients with active, ANA lupus (SLE) who are receiving standard therapy, including corticosteroids, antimalarials, immunosuppressives, and nonsteroidal anti-inflammatory drugs.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, FDA approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, Blue Cross and Blue Shield Association technology assessment program (TEC) and other non-affiliated technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

Intravenous
The safety and effectiveness of Benlysta administered IV plus standard therapy were evaluated in 3 randomized, double-blind, placebo-controlled trials involving 2,133 patients with SLE. Patients with severe active lupus nephritis and severe active 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, NSAIDs, and immunosuppressives. Use of other biologics and IV cyclophosphamide were not permitted.

Trial 1 enrolled 449 patients and evaluated doses of 1, 4, and 10 mg/kg Belysta plus standard therapy compared with placebo plus standard therapy over 52 weeks in patients with SLE. The co-primary endpoints were percent change in Safety of Estrogens in Lupus Erythematosus National Assessment-Systemic Lupus Erythematosus Disease Activity Index (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 ANA SLE patients.

Trials 2 and 3 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. 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. The SRI uses the SELENA-SLEDAI score as an objective measure of reduction in global disease activity; the BILAG index to ensure no significant worsening in any specific organ system; and the PGA to ensure that improvements in disease activity are not accompanied by worsening of the patient's condition overall.

In both Trials 2 and 3, the proportion of patients with SLE achieving an SLE Responder Index-4 (SRI-4), 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 (43% vs. 34%, P=0.021 in trial 2 and 58% vs. 44%, P<0.001 in trial 3). 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).

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). Although no definitive conclusion can be drawn from this subgroup analysis, caution should be used when considering treatment with Benlysta in black/African-American patients.

Subcutaneous

The safety and effectiveness of Benlysta administered subcutaneously were evaluated in a randomized, double-blind, placebo-controlled trial involving 836 patients with SLE. Patients with severe active lupus nephritis and severe active CNS lupus were excluded. The trial evaluated Benlysta 200 mg once weekly

plus standard therapy (n = 556) compared with placebo once weekly plus standard therapy (n = 280) over 52 weeks in patients with active SLE disease.

The primary efficacy endpoint was the SRI-4 at Week 52 as described in the IV trials. The proportion of patients achieving an SRI-4 response was significantly higher in patients receiving Benlysta plus standard therapy compared with placebo plus standard therapy (61% vs. 48%, P=0.0006). The trends comparing the treatment groups with respect to the probability of response for the individual components of the endpoint were consistent with that of the SRI-4.

Exploratory sub-group analyses of SRI-4 response rate in black patients (n = 91) were performed. The SRI-4 response rate was slightly higher in black patients receiving Benlysta plus standard therapy (26/58 or 45%) compared with the group receiving placebo plus standard therapy (13/33 or 39%), but the treatment difference was not as large as that observed in the overall population and no definitive conclusion can be drawn from this subgroup analysis. Caution should be used when considering treatment with Benlysta in black/African-American patients.

References

1. Benlysta [package insert]. GlaxoSmithKline. Research Triangle Park, North Carolina. Updated July 2017.
2. UpToDate. Systemic Lupus Erythematosus. Accessed 4/10/2018.

Policy History

Original Effective Date: 04/13/2011
Current Effective Date: 05/16/2018

04/07/2011	Medical Policy Committee review
04/13/2011	Medical Policy Implementation Committee approval. New policy
04/12/2012	Medical Policy Committee review
04/25/2012	Medical Policy Implementation Committee approval.
04/04/2013	Medical Policy Committee review
04/24/2013	Medical Policy Implementation Committee approval. No changes to coverage. A few cosmetic changes. Consolidated the When Services Are Considered Investigational section.
05/01/2014	Medical Policy Committee review
05/21/2014	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
05/07/2015	Medical Policy Committee review
05/20/2015	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/03/2015	Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
05/05/2016	Medical Policy Committee review
05/18/2016	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
05/04/2017	Medical Policy Committee review
05/17/2017	Medical Policy Implementation Committee approval. Coverage eligibility unchanged
05/03/2018	Medical Policy Committee review
05/16/2018	Medical Policy Implementation Committee approval. Updated background information and rationale.

Next Scheduled Review Date: 05/2019

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Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2017 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	No codes
HCPCS	J0490
ICD-10 Diagnosis	M32.0, M32.10-M32.19, M32.8-M32.9

*****Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

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