09-J1000-35

Original Effective Date: 08/15/11

Reviewed: 11/09/22

Revised:10/15/23

Next Review: 10/11/23

Subject: Belimumab (Benlysta®) Injection

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/O2R INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

DESCRIPTION:

Belimumab (Benlysta) is a human monoclonal antibody that inhibits B lymphocyte stimulator protein (BLyS). In March 2011, belimumab was approved the US Food and Drug Administration (FDA) for the treatment of active, autoantibody positive systemic lupus erythematosus (SLE). Belimumab was originally approved as an intravenous injection, but a subcutaneous formulation was was approved in 2017. Belimumab should be used as an adjunct to standard therapy. SLE is a chronic inflammatory disease of unknown cause that can affect multiple systems including the musculoskeletal, renal, pulmonary, gastrointestinal, and hematologic systems. The etiology of SLE is not completely understood; however, many of the clinical manifestations are mediated directly or indirectly by antibody formation and the creation of immune complexes.

Diagnosis of SLE is based on classification criteria developed by the American Rheumatism Association (now the American College of Rheumatology [ACR]) that uses history, physical examination, and laboratory data for diagnosis. Several disease activity instruments are used in clinical trials. The Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) is comprised of 24 clinical and laboratory manifestations of SLE that are scored based on presence or absence in the previous 10 days. Organ involvement is weighted and the final score can range from 0-105. A SLEDAI score of 6 or more has been shown to be consistent with active disease requiring therapy. The SLEDAI was modified in the Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA) trial; this modification, known as SELENA-SLEDAI added clarity to some of the definition of activity in the individual items but did not change the basic scoring system. A clinically meaningful difference has been reported to be an improvement of 7 points or a worsening of 8 points. The British Isles Lupus Assessment Group (BILAG) is an organ specific, 86 question assessment based on the healthcare provider's intention to treat. The

assessor scores organ manifestations as improve (=1), same (=2), worse (=3), or new (=4) over the last month.

POSITION STATEMENT:

Site of Care

If intravenous belimumab (Benlysta) is administered in a hospital-affiliated outpatient setting, additional requirements may apply depending on the member's benefit. Refer to 09-J3000-46: Site of Care Policy for Select Specialty Medications.

Comparative Effectiveness

The Food and Drug Administration has deemed the drug(s) or biological product(s) in this coverage policy to be appropriate for self-administration or administration by a caregiver (i.e., not a healthcare professional). Therefore, coverage (i.e., administration) in a provider-administered setting such as an outpatient hospital, ambulatory surgical suite, or emergency facility is not considered medically necessary. This statement applies to Benlysta for subcutaneous administration only.

Initiation of belimumab (Benlysta®) meets the definition of medical necessity when used for for members diagnosed with ANY of the following conditions when ALL associated criteria are met:

1. Systemic lupus erythematosus (SLE)
    a. Member's disease is active as evidenced by Safety of Estrogens in Lupus Erythematosus National Assessment modification of the SLE Disease Activity Index (SELENA-SLEDAI) score of 6 or greater while on current regimen.

       NOTE: SELENA-SLEDAI scoring system can be located at www.rheumatology.org

    b. Laboratory testing has demonstrated the presence of autoantibodies [e.g., ANA, Anti-dsDNA, Anti-Sm, Anti-Ro/SSA, Anti-La/SSB]
    c. Member is currently receiving standard of care SLE treatment including one or more of the following
        i. Corticosteroids (e.g., prednisone)
        ii. Aspirin
        iii. Non-steroidal anti-inflammatory drug (NSAID)
        iv. Anti-malarials (e.g., hydroxychloroquine, chloroquine)
        v. Non-biologic immunosuppressants (e.g., azathioprine, methotrexate, cyclosporine, oral cyclophosphamide)
    d. There is no evidence of active central nervous system lupus (e.g., psychosis, seizures, cerebrovascular accident) within the past 60 days
    e. Belimumab is not used in combination with other biologic DMARD therapies (e.g., abatacept (Orencia), adalimumab (Humira), anakinra (Kineret), certolizumab (Cimzia), etanercept (Enbrel), etanercept-szzs (Ereizi), golimumab (Simponi, Simponi Aria), and infliximab (Remicade))

f. Member is 5 years of age or older

g. The dose does not exceed **EITHER** of the following

i. IV injection:

1. First 6 weeks: 10 mg/kg every 2 weeks for 3 doses
2. Thereafter: 10 mg/kg every 4 weeks

ii. SC injection: 200 mg once weekly

2. Lupus Nephritis

a. Member's disease is active as evidenced by Safety of Estrogens in Lupus Erythematosus National Assessment modification of the SLE Disease Activity Index (SELENA-SLEDAI) score of 6 or greater while on current regimen.

NOTE: SELENA-SLEDAI scoring system can be located at www.rheumatology.org

b. Laboratory testing has demonstrated the presence of autoantibodies [e.g., ANA, Anti-dsDNA, Anti-Sm, Anti-Ro/SSA, Anti-La/SSB]

c. Member has biopsy-proven lupus nephritis of International Society of Nephrology and Renal Pathology Society class III (focal lupus nephritis) or IV (diffuse lupus nephritis) with or without coexisting class V (membranous lupus nephritis), or pure class V lupus nephritis – laboratory documentation must be provided

d. Member is currently receiving standard of care SLE treatment including one or more of the following

i. Corticosteroids (e.g., prednisone)

ii. Aspirin

iii. Non-steroidal anti-inflammatory drug (NSAID)

iv. Anti-malarials (e.g., hydroxychloroquine, chloroquine)

v. Non-biologic immunosuppressants (e.g., azathioprine, methotrexate, cyclosporine, cyclophosphamide)

e. There is no evidence of active central nervous system lupus (e.g., psychosis, seizures, cerebrovascular accident) within the past 60 days

f. Belimumab is not used in combination with other biologic DMARD therapies (e.g., abatacept (Orencia), adalimumab (Humira), anakinra (Kineret), certolizumab (Cimzia), etanercept (Enbrel), etanercept-szzs (Ereizi), golimumab (Simponi, Simponi Aria), and infliximab (Remicade))

g. Belimumab is not used in combination with voclosporin (Lupkynis) or anifrolumab-fnia (Saphnelo)

h. Member is 5 years of age or older

i. The dose does not exceed **EITHER** of the following

i. IV injection:

1. First 6 weeks: 10 mg/kg every 2 weeks for 3 doses

2. Thereafter: 10 mg/kg every 4 weeks

ii. SC injection:

1. First 4 weeks: 400 mg once weekly for 4 doses
2. Thereafter: 200 mg once weekly

3. Other FDA-approved or NCCN supported diagnosis (not previously listed above)
   a. Member meets one of the following:
      i. Member is diagnosed with a condition that is consistent with an indication listed in the product's FDA-approved prescribing information (or package insert) AND member meets any additional requirements listed in the "Indications and Usage" section of the FDA-approved prescribing information (or package insert)
      ii. Indication AND usage is recognized in NCCN Drugs and Biologics Compendium as a Category 1 or 2A recommendation
   b. Dose does not exceed maximum FDA-approved dose and frequency

Approval duration: 6 months

Continuation of belimumab (Benlysta®) meets the definition of **medical necessity** when **ALL** of the following criteria are met:

1. Member has been approved by another healthplan or met Florida Blue's initial criteria for coverage
2. Member has demonstrated a beneficial response with belimumab therapy for the treatment of active systemic lupus erythematosus, lupus nephritis, or other FDA-approved or NCCN supported diagnosis
3. Belimumab is not used in combination with another biologic DMARD therapy (e.g., abatacept (Orencia), adalimumab (Humira), anakinra (Kineret), certolizumab (Cimzia), etanercept (Enbrel), etanercept-szzs (Ereizi), golimumab (Simponi, Simponi Aria), and infliximab (Remicade))
4. If for lupus nephritis, belimumab is not used in combination with voclosporin (Lupkynis) or anifrolumab-fnia (Saphnelo)
5. The dose does not exceed **EITHER** of the following:
   a. IV injection:10 mg/kg every 4 weeks
   b. SC injection: 200 mg once weekly

Approval duration: 1 year

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved:

- Intravenous Administration
    - 10 mg/kg at 2-week intervals for the first 3 doses and at 4-week intervals thereafter. Reconstitute, dilute, and administer as an intravenous infusion over a period of 1 hour.
    - Consider administering premedication for prophylaxis against infusion reactions and hypersensitivity reactions.
- Subcutaneous Administration (18 years of age and older)
    - 200 mg once weekly.

Drug Availability:

- IV infusion: 120 mg or 400 mg lyophilized powder in single-dose vials for reconstitution and dilution prior to intravenous infusion
- Subcutaneous injection: 200 mg/mL single-dose prefilled autoinjector or single-dose prefilled syringe

PRECAUTIONS:

CONTRAINDICATION: belimumab is contraindicated in persons who experienced a previous anaphylactic reaction when administered belimumab.

WARNINGS/PRECAUTIONS:

Mortality: more deaths were reported with belimumab than with placebo during the controlled phase of clinical trials.

Serious infections: serious and sometimes fatal infections have been reported in persons receiving immunosuppressive agents, including belimumab. Use with caution in persons with chronic infections. Consider interrupting belimumab therapy if a member develops a new infection while on treatment.

Progressive Multifocal Leukoencephalopathy (PML): Persons with new-onset or deteriorating neurological signs and symptoms should be evaluated for PML by an appropriate specialist. If PML is confirmed, considered discontinuing immunosuppressant therapy, including belimumab.

Hypersensitivity reactions: serious and fata reactions have been reported. Belimumab should be administered by a healthcare provider prepared to manage anaphylaxis. Monitor members during and for an appropriate period of time after belimumab administration.

Depression: depression and suicidality have been reported in belimumab studies. Members should be instructed to contact their healthcare provider f they experience new or worsening depression, suicidal thoughts, or other mood changes.

Immunization: live vaccines should not be given concurrently with belimumab.

BILLING/CODING INFORMATION:

HCPCS Coding:

J0490	Injection, belimumab, 10 mg

ICD-10 Diagnosis Codes That Support Medical Necessity:

M32.10 – M32.9	Systemic lupus erythematosus, organ or system involvement unspecified

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Advantage Products: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline revised date. The Site of Care Policy for Select Specialty Medications does not apply to Medicare Advantage members.

DEFINITIONS:

Systemic lupus erythematosus: is a systemic autoimmune disease than can affect any part of the body. As occurs in other autoimmune diseases, the immune system attacks the body's cells and tissue, resulting in inflammation and tissue damage.

RELATED GUIDELINES:

None

OTHER:

None

REFERENCES:

1. Clinical Pharmacology [Internet]. Tampa (FL): Gold Standard, Inc.; 2022 [cited 10/28/22]. Available from: http://www.clinicalpharmacology.com/.
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4. Human Genome Sciences. Benlysta (belimumab) injection. 2019 [cited 10/28/22]. In: DailyMed [Internet]. Bethesda (MD): National Library of Medicine. Available from: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=2fa3c528-1777-4628-8a55-a69dae2381a3
5. Orphan Drug Designations and Approval [Internet]. Silver Spring (MD): US Food and Drug Administration; 2022 [cited 10/28/22]. Available from: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm/.

COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 09/13/23.

GUIDELINE UPDATE INFORMATION:

08/15/11	New Pharmacy Coverage Guideline.
01/01/12	Revision to guideline; consisting of updating codes.
08/15/12	Review and revision to guideline; consisting of updating position statement, precautions and references.
12/15/12	Revision to guideline; consisting of modifying continuation criteria.
08/15/13	Review and revision to guideline; consisting of reformatting position statement, dosage/administration, and precautions sections; revised description section and updated references.
08/15/14	Review and revision to guideline; consisting of updating position statement, precautions and references.
11/01/15	Revision: ICD-9 Codes deleted.
11/15/17	Revision to guideline to include SC formulation in position statement, dosing and administration, references.
08/15/19	Revision to position statement to include updated age restrictions.
09/15/19	Revision to position statement to clarify approval duration of 6 months.
01/15/20	Review and revision to guideline; consisting of updating references.
03/15/21	Revision to position statement to include standard statement regarding FDA approved indications.
04/15/21	Revision to position statement to include lupus nephritis .
12/15/22	Review and revision to guideline; consisting of updating references and position statement.
10/15/23	Revision to position statement.