Corporate Medical Policy

Belimumab (Benlysta)

File Name:	belimumab_benlysta
Origination:	6/2011
Last CAP Review:	1/2021
Next CAP Review:	1/2022
Last Review:	2/2021

Description of Procedure or Service

Belimumab (Benlysta) is a human monoclonal antibody drug that specifically recognizes and inhibits the biological activity of B-lymphocyte stimulator, or BLyS. BLyS is a cytokine that belongs to the tumor necrosis factor (TNF) ligand family. It is expressed as a transmembrane protein on various cell types including monocytes, dendritic cells, and bone marrow stromal cells and is required for the development of B-lymphocyte cells into mature plasma B cells. Plasma B cells produce anti-bodies, the body's first line of defense against infection. In lupus and certain other autoimmune diseases, elevated levels of BLyS are believed to contribute to the production of autoantibodies, which are antibodies that attack and destroy the body's own healthy tissues. The presence of autoantibodies appears to correlate with disease severity. Preclinical and clinical studies suggest that belimumab can reduce autoantibody levels in SLE. Benlysta (belimumab) has been approved by the U.S. Food and Drug Administration (FDA) for the adjunctive treatment of active, autoantibody-positive, systemic lupus erythematosus (SLE). It was originally approved as an intravenous infusion, but a subcutaneous formulation was approved in 2017. The intravenous infusion is indicated for patients aged 5 years and older, and the subcutaneous injection is indicated for patients aged 18 years and older. In December 2020, Benlysta also received FDA approval for the treatment of adult patients with active lupus nephritis who are receiving standard therapy.

Systemic lupus erythematosus (SLE) is a potentially fatal autoimmune disease that is characterized by clinical diversity, alterations in disease activity over time, and aberrations in multiple immune system components including B cells, T cells, as well as cytokines and growth factors, especially the presence of anti-nuclear antibodies (ANA) found in over 90 % of patients. Moreover, anti-double-strand deoxyribonucleic acid (anti-dsDNA) antibodies are found in 50 to 90 % of patients. The disease affects many parts of the body including the brain, heart, joints, kidneys, lungs, and skin. When SLE flares, it can present as chest pain, fatigue, fever, hair loss, rash, light sensitivity, as well as joint pain and swelling. Conventional treatments of SLE include anti-malarials (e.g., chloroquine and hydroxychloroquine), corticosteroids, and non-steroidal anti-inflammatory drugs (e.g., aspirin). While therapeutic advances in immunosuppressive drugs (e.g., azathioprine, cyclophosphamide, methotrexate, mycophenolate) and support therapy have markedly improved survival, SLE still carries substantially increased rates of mortality and end stage renal disease, which are even more elevated in younger patients.

******Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

Policy

BCBSNC will provide coverage for belimumab (Benlysta) when it is determined to be medically necessary because the medical criteria and guidelines shown below are met.

Belimumab (Benlysta)

Coverage for belimumab (Benlysta) requires prior review.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy

When Belimumab (Benlysta) is covered

Belimumab may be considered medically necessary when the following criteria are met:

1. The patient has a clinical diagnosis of systemic lupus erythematosus (SLE); **AND**

    a. All of the following:
        i. The patient is 5 years of age or older; **AND**
        ii. The patient is autoantibody-positive with ONE of the following:
            1. Anti-nuclear antibody (ANA) titer ≥ 1:80, **or**
            2. Anti-doublestranded DNA (anti-dsDNA) level ≥ 30 IU/mL]; **AND**
        iii. SLE is active, demonstrated by a score greater than 6 (as documented by a SELENA-SLEDAI) while on treatment with standard therapy (e.g., corticosteroids, aspirin, non-steroidal anti-inflammatory drugs [NSAIDs], anti-malarials [hydroxychloroquine, chloroquine], or non-biologic immunosuppressants [azathioprine, methotrexate, cyclosporine, oral cyclophosphamide]), alone or as combination therapy; **AND**
        iv. There is no evidence of renal disease (e.g., on dialysis, proteinuria > 6 g/day, or creatinine > 2.5 mg/dL) and/or central nervous system disease (seizures, psychosis, etc.);
        OR
    b. The patient has biopsy-proven lupus nephritis Class III, IV, and/or V; **AND**
        i. The patient is 18 years of age or older; **AND**
        ii. The patient has active renal disease requiring standard therapy of corticosteroids with mycophenolate for induction and maintenance or cyclophosphamide for induction followed by azathioprine for maintenance; **AND**

2. The patient will continue standard therapy (e.g., corticosteroids, antimalarials, NSAIDs, and immunosuppressives).

When Belimumab (Benlysta) is not covered

Belimumab is considered **investigational** for all other indications not listed above.

Belimumab is considered not medically necessary for use in patients with severe active central nervous system lupus.

Belimumab is considered not medically necessary when used in combination with other biologics or intravenous cyclophosphamide.

Policy Guidelines

The efficacy of belimumab has not been evaluated in patients with severe active central nervous system lupus. Belimumab has not been studied in combination with other biologics or intravenous cyclophosphamide.

Serious and sometimes fatal infections have been reported in patients receiving immuno-suppressive agents, including belimumab (Benlysta). Caution should be exercised when considering use in patients with a history of chronic infections. Patients receiving therapy for a chronic infection should not receive belimumab (Benlysta). Patients presenting with new-onset or deteriorating neurological signs and symptoms should be evaluated for Progressive Multifocal Leukoencephalopathy (PML) by an appropriate specialist. If PML is confirmed, discontinuation of immunosuppressant therapy, including belimumab (Benlysta) should be considered.

Acute hypersensitivity reactions, including anaphylaxis and death, have been reported in association with belimumab (Benlysta). These events generally occurred within hours of the infusion; however, they may occur later. Non-acute hypersensitivity reactions including rash, nausea, fatigue, myalgia, headache, and facial edema, have been reported and typically occurred up to a week following the most recent infusion. Hypersensitivity, including serious reactions, has occurred in patients who have previously tolerated infusions of belimumab (Benlysta). Patients with a history of multiple drug allergies may be at increased risk of hypersensitivity/anaphylaxis.

Belimumab is approved as an intravenous infusion in patients 5 years and older with active, autoantibody-positive systemic lupus erythematosus and in patients 18 years and older with active lupus nephritis. Belimumab is also approved as a subcutaneous injection in patients aged 18 years and older.

There are no adequate and well-controlled clinical studies using belimumab (Benlysta) in pregnant women. Benlysta should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus. Women of childbearing potential should use adequate contraception during treatment and for at least 4 months after the final treatment. Because maternal antibodies are excreted in human breast milk, a decision should be made whether to discontinue breast-feeding or to discontinue the drug, taking into account the importance of breastfeeding to the infant and the importance of the drug to the mother.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: *J0490*

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

U.S. Food and Drug Administration (FDA). Belimumab (Benlysta) injection. Highlights of prescribing information. March 2011. Available at:

http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/125370s0000lbl.pdf

Benlysta (belimumab). Product information. GlaxoSmithKline 2011.

Specialty Matched Consultant Advisory Panel- 2/2012

U.S. Food and Drug Administration (FDA). Belimumab (Benlysta) injection. Highlights of prescribing information. March 2011. Available at:
http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/125370s0000lbl.pdf
Last accessed January 2014.

Specialty Matched Consultant Advisory Panel- 2/2013

U.S.Food and Drug Administration (FDA). Belimumab (Benlysta). Safety information. December 2013. Available at:
http://www.fda.gov/safety/medwatch/safetyinformation/ucm299628.htm

Specialty Matched Consultant Advisory Panel- 2/2014

Specialty Matched Consultant Advisory Panel- 2/2015

Specialty Matched Consultant Advisory Panel- 2/2016

1997 Update of the 1982 American College of Rheumatology Revised Criteria for Classification of Systemic Lupus Erythematosus available at: http://www.rheumatology.org

U.S. Food and Drug Administration (FDA). Belimumab (Benlysta) injection. Highlights of prescribing information. July 2017. Available at:
https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125370s057lbl.pdf
Last accessed March 2018.

Medical Director review 3/2018

Specialty Matched Consultant Advisory Panel- 2/2019

GlaxoSmithKline. Benlysta (belimumab) for injection for intravenous use and subcutaneous use. Highlights of prescribing information. January 2020. Available at:
https://www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Benlysta/pdf/BENLYSTA-PI-MG-IFU-COMBINED.PDF. Last accessed January 2020.

Specialty Matched Consultant Advisory Panel- 2/2020

GlaxoSmithKline. Benlysta (belimumab) for injection for intravenous use and subcutaneous use. Highlights of prescribing information. December 2020. Available at:
https://www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Benlysta/pdf/BENLYSTA-PI-MG-IFU.PDF. Last accessed January 2021.

Medical Director review 1/2021

Blue Cross NC Pharmacy and Therapeutics Committee 1/2021

Medical Director review 2/2021

Policy Implementation/Update Information

7/1/11 New medical policy issued. Belimumab is considered medically necessary for treatment of active, autoantibody-positive, systemic lupus erythematosus. Notification date 7/1/2011 for effective date 10/1/2011. PPA implementation 10/1/2011. Medical director review 6/2011. (lpr)

12/6/11 Deleted statement: "who are not immunocompromised" under When Covered section. Added statement: "Serious and sometimes fatal infections have been reported in patients receiving immunosuppressive agents, including Benlysta. Caution should be exercised when considering use in patients with a history of chronic infections. Patients receiving therapy for a chronic infection should not receive Benlysta" to Policy Guidelines section. Reviewed with medical director. Removed HCPCS code Q2044 from the Billing/Coding section and added J0490 effective 1/1/2012. (lpr)

3/20/12 Under "When Not Covered" first two statements changed to read "not medically necessary" Instead of "investigational" and the last statement continues to read "investigational for all other indications, including but not limited to use in children." Specialty Matched Consultant Advisory Panel review meeting 2/29/12. No change to policy statement. (lpr)

3/12/13 Specialty Matched Consultant Advisory Panel review meeting 2/20/2013. No change to policy statement. Reference added. (lpr)

4/1/14 Specialty Matched Consultant Advisory Panel review meeting 2/25/2014. Updated Policy Guidelines section. Reference updated. (lpr)

3/10/15 Specialty Matched consultant advisory panel review meeting 2/5/2015. No change to policy statement. (lpr)

4/1/16 Specialty Matched consultant advisory panel review meeting 2/24/16. No change to policy statement. –an

12/30/16 Minor changes to description section. No change to policy statement. (an)

3/31/17 Description section updated. Added specific laboratory findings to Item 2 in the When Covered section. Information regarding use during pregnancy and lactation added to Policy Guidelines section. Reference added. Specialty Matched Consultant Advisory Panel review meeting 2/22/2017. (an)

4/13/18 Under "When Covered" section, added "AND" after Item 2 and added the following statement as Item 3 pertaining to Belimumab (Benlysta) indication for the treatment of adult patients with active, autoantibody-positive, systemic lupus erythematosus **who are receiving standard therapy**: "With failure or inadequate response to standard therapy at the time of belimumab initiation. Standard therapy includes one or more of the following:". Also added list of drugs that are considered standard treatment for SLE. Minor typographical errors corrected and additions made to Policy Guidelines section for clarity. References added. Specialty Matched Consultant Advisory Panel review meeting 2/28/2018. Medical Director review. **Notification given 4/13/18 for policy effective date 7/12/18.** (krc)

3/12/19 Specialty Matched Consultant Advisory Panel review 2/20/2019. No change to policy statement. (krc)

3/10/20 Updated "When Covered" section to "5 years of age or older". Under "When Not Covered," removed investigational statement for use in children and reorganized criteria formatting for clarity. Added statements in Description and Policy Guidelines sections to reflect approval of IV infusion in patients aged 5 years and older, and

subcutaneous injection in patients aged 18 years and older Reference added. Specialty Matched Consultant Advisory Panel review 2/19/2020. (krc)

1/26/21 Under "When Covered" section, added coverage for FDA approved indication for adult patients with active lupus nephritis who are receiving standard therapy, when specific criteria are met for new indication. Reference added. Blue Cross NC Pharmacy and Therapeutics Committee 1/5/2021. Medical Director review 1/2021. (krc)

2/9/21 Minor updates made to policy for clarity. Medical Director review 2/2021.