Medical Policy Bulletin
Title:
Belimumab (Benlysta®) for Intravenous Use
Policy #:
MA08.057d

The Company makes decisions on coverage based on the Centers for Medicare and Medicaid Services (CMS) regulations and guidance, benefit plan documents and contracts, and the member's medical history and condition. If CMS does not have a position addressing a service, the Company makes decisions based on Company Policy Bulletins. Benefits may vary based on contract, and individual member benefits must be verified. The Company determines medical necessity only if the benefit exists and no contract exclusions are applicable. Although the Medicare Advantage Policy Bulletin is consistent with Medicare's regulations and guidance, the Company's payment methodology may differ from Medicare.

When services can be administered in various settings, the Company reserves the right to reimburse only those services that are furnished in the most appropriate and cost-effective setting that is appropriate to the member's medical needs and condition. This decision is based on the member's current medical condition and any required monitoring or additional services that may coincide with the delivery of this service.

This Policy Bulletin document describes the status of CMS coverage, medical terminology, and/or benefit plan documents and contracts at the time the document was developed. This Policy Bulletin will be reviewed regularly and be updated as Medicare changes their regulations and guidance, scientific and medical literature becomes available, and/or the benefit plan documents and/or contracts are changed.

Policy

Coverage is subject to the terms, conditions, and limitations of the member's Evidence of Coverage.

The Company reserves the right to reimburse only those services that are furnished in the most appropriate and cost-effective setting that is appropriate to the member's medical needs and condition.

MEDICALLY NECESSARY

SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)
Belimumab (Benlysta) for **intravenous** use is considered medically necessary and, therefore, covered when used for the treatment of individuals with systemic lupus erythematosus (SLE) five years of age and older who meet **all** of the following criteria:

- Active systemic lupus erythematosus (SLE)
- Positive autoantibody test (e.g., antinuclear antibody test [ANA], antibodies to DNA [Anti-dsDNA], Anti-Smith [Anti-Sm])
- Concurrent treatment with at least one of the following: steroids, antimalarials, immunosuppressives, or nonsteroidal anti-inflammatory drugs (NSAIDS)

LUPUS NEPHRITIS (LN)
Belimumab (Benlysta) for **intravenous** use is considered medically necessary and, therefore, covered when used for the treatment of individuals with lupus nephritis (LN) five years of age and older who meet **all** of the following criteria:

- Active systemic lupus erythematosus
- Biopsy-proven lupus nephritis Class III, IV, and/or V and have active renal disease at screening
- Concurrent standard treatment for lupus nephritis (e.g. corticosteroids along with one of the following regimens: mycophenolate for induction followed by mycophenolate for maintenance or cyclophosphamide for induction followed by azathioprine for maintenance)

EXPERIMENTAL/INVESTIGATIONAL

Belimumab (Benlysta) for intravenous use is considered experimental/investigational and, therefore, not covered because the safety and/or effectiveness of this service cannot be established by review of the available published peer-reviewed literature in the following clinical circumstances:

- In individuals with severe, active central nervous system lupus
- In combination with other biologics or B-cell-targeted therapies

Any use of belimumab (Benlysta) for intravenous use that is not supported in either this medical policy or the off-label coverage policy is considered experimental/investigational and, therefore, not covered.

REQUIRED DOCUMENTATION

The individual's medical record must reflect the medical necessity for the care provided. These medical records may include, but are not limited to: records from the professional provider's office, hospital, nursing home, home health agencies, therapies, and test reports.

The Company may conduct reviews and audits of services to our members, regardless of the participation status of the provider. All documentation is to be available to the Company upon request. Failure to produce the requested information may result in a denial for the drug.

BILLING REQUIREMENTS

For drugs that have more than one method of administration, application of the JA modifier is required to indicate the route of administration.
To report the intravenous route of administration, append the following modifier: JA Administered Intravenously

Inclusion of a code in this policy does not imply reimbursement. Eligibility, benefits, limitations, exclusions, utilization management/referral requirements, provider contracts, and Company policies apply.

Guidelines

This policy is consistent with Medicare’s coverage determination. The Company’s payment methodology may differ from Medicare.

BENEFIT APPLICATION

Subject to the terms and conditions of the applicable Evidence of Coverage, belimumab (Benlysta) for intravenous use is covered under the medical benefits of the Company's Medicare Advantage products when the medical necessity criteria listed in this medical policy are met.

However, services that are identified in this policy as experimental/investigational are not eligible for coverage or reimbursement by the Company.

Certain drugs are available through either the member's medical benefit (Part B benefit) or the pharmacy benefit (Part D benefit), depending on how the drug is prescribed, dispensed, or administered. This medical policy only addresses instances when belimumab (Benlysta) for intravenous use is covered under a member's medical benefit (Part B benefit). It does not address instances when belimumab (Benlysta) for intravenous use is covered under a member's pharmacy benefit (Part D benefit).

US FOOD AND DRUG ADMINISTRATION (FDA) STATUS

Belimumab (Benlysta) for intravenous use was approved by the FDA on March 9, 2011 for the treatment of adult patients with active, autoantibody-positive, systemic lupus erythematosus who are receiving standard therapy. Supplemental approvals for belimumab (Benlysta) for intravenous use have since been issued by the FDA. The efficacy of belimumab (Benlysta) for intravenous use has not been evaluated in individuals with severe active central nervous system lupus. The safety and efficacy of belimumab (Benlysta) for intravenous use has not been shown in combination with other biologics. Use of belimumab (Benlysta) for intravenous use is not recommended in these situations.

PEDIATRIC INDIVIDUALS
Intravenous administration of belimumab (Benlysta) is indicated in individuals aged five years and older with systemic lupus erythematosus; its safety and effectiveness have not been established in pediatric individuals younger than five years of age. The safety and effectiveness of intravenous administration of blimumab (Benlysta) have been established in pediatric individuals with active lupus nephritis age five years and older. Subcutaneous dosing of belimumab (Benlysta) has not been evaluated and is not approved for pediatric individuals younger than 18 years of age.

Description

SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by periods of illness and remissions in which the immune system produces antibodies to cells within the body leading to widespread inflammation and tissue damage. Immunologic abnormalities, especially the production of a number of antinuclear antibodies (ANA), are a prominent feature of the disease. SLE has a variety of clinical manifestations, and it can affect joints, skin, brain, lungs, kidneys, and blood vessels. Individuals with SLE may experience fatigue, pain or swelling in joints, skin rashes, and fevers.

On March 9, 2011, the US Food and Drug Administration (FDA) approved belimumab (Benlysta) for intravenous (IV) use in individuals with active, autoantibody-positive SLE who are receiving standard therapy, including corticosteroids, antimalarials, immunosuppressives, and nonsteroidal anti-inflammatory drugs (NSAIDs). It is the first inhibitor intended to target B-lymphocyte stimulator (BLyS) protein, which may reduce the number of abnormal B cells. BLyS is overexpressed in patients with SLE and other autoimmune diseases. After subsequent studies using the IV formulation, the FDA granted approval in pediatric individuals age five years and older. Additionally, a subcutaneous formulation of belimumab (Benlysta) for use in adults was also FDA approved.

LUPUS NEPHRITIS (LN)

Lupus nephritis (LN) is the most common organ-threatening manifestation of SLE and can result in significant morbidity and mortality. It adversely affects individuals with SLE in terms of individual and renal survival rates as well as quality of life and work disability. Improved outcomes in members with LN can result from treatment of both the underlying SLE as well as the renal disease. The presence of renal disease can be demonstrated with multiple methods including serum and urine laboratory tests. The presence of nephritis can be identified with a kidney biopsy. Standard therapy includes treatment with corticosteroids along with induction and maintenance medications. On December 16, 2020, the FDA approved belimumab (Benlysta) for IV use in individuals, age 18 and older, with active LN who are receiving standard therapy, which can include corticosteroids with 1) mycophenolate for induction followed by mycophenolate for maintenance, or 2) cyclophosphamide for induction followed by azathioprine for maintenance.

PEER-REVIEWED LITERATURE

SUMMARY

Systemic Lupus Erythematosus (SLE)

Two clinical studies involving 1,684 individuals with lupus demonstrated the safety and effectiveness of belimumab (Benlysta) for IV use. The studies diagnosed individuals with active lupus and randomized them to receive belimumab (Benlysta) for IV use plus standard therapy, or an inactive infused solution (placebo) plus standard therapy. The studies excluded anyone who had received prior B-cell targeted therapy or IV cyclophosphamide, and those who had active lupus involving the kidneys or central nervous system.

The individuals treated with belimumab (Benlysta) for IV use and standard therapies experienced less disease activity than those who received a placebo and standard-of-care medicines. Results suggested, but did not definitively establish, that some patients had a reduced likelihood of severe flares, and some reduced their steroid doses.

Subsequent safety and efficacy results for subjects treated up to seven years continue to support disease control and safety profile in individuals with active SLE taking belimumab (Benlysta) plus standard therapy.

The safety and efficacy of the use of IV belimumab (Benlysta) in pediatric individuals was evaluated in a phase 2, randomized, placebo-controlled, double-blind study involving 93 participants. These participants were divided into 3 cohorts. Cohort 1 enrolled 12 individuals ages 12 to 17, in a 5:1 ratio, to receive belimumab (Benlysta) or placebo on days 0, 14, 28, then every 28 days until week 48. The pharmacokinetics of the drug in the pediatric individuals were compared to the pharmacokinetics of the drug in adult individuals from previous clinical trials. When it was confirmed that these were similar, Cohorts 2 and 3 began to enroll. In Cohort 2, 13 individuals ages 5 to 11 years were enrolled in a 5:1 ratio to receive belimumab (Benlysta) or placebo in the same manner as Cohort 1. Cohort 3 enrolled 68 pediatric individuals ages 5 to 17 and randomized them 1:1 to receive belimumab (Benlysta) or placebo according to age and Safety of Estrogens in Lupus Erythematosus National Assessment-SLE Disease Activity Index (SELENA-SLEDAI) scores. The primary efficacy endpoint was the SLE Responder Index (SRI-4) score at week 52. Some secondary endpoints included change in SELENA-SLEDAI scores by week 52, change in proteinuria, and adverse

events. Because of the difficulty in enrolling enough participants to enable significance levels, the results were discussed descriptively. The percentage of individuals who experienced a 4 or more point reduction in SELENA-SLEDAI scores was 55 percent for the belimumab (Benlysta) group and 44 percent for the placebo group. The number of individuals with higher levels of proteinuria was 1.43 for the belimumab (Benlysta) group and 6.13 for the placebo group. The incidence of adverse events were similar between the treatment group and the placebo group with 79.2 percent versus 82.5 percent, respectively. One death occurred in the placebo group, but none in the treatment group.

Lupus Nephritis (LN)

A clinical study involving 448 individuals with active proliferative and/or membranous LN demonstrated the safety and effectiveness of belimumab (Benlysta) for IV use. The individuals had a clinical diagnosis of SLE according to American College of Rheumatology classification criteria; biopsy-proven LN Class III, IV, and/or V; and had active renal disease at screening requiring standard therapy: corticosteroids with 1) mycophenolate for induction followed by mycophenolate for maintenance, or 2) cyclophosphamide for induction followed by azathioprine for maintenance.

The proportion of individuals achieving Primary Efficacy Renal Response (PERR) at week 104 was significantly higher in individuals receiving belimumab (Benlysta) plus standard therapy compare with placebo plus standard therapy (p=0.031). The major secondary endpoints also showed significant improvement with belimumab (Benlysta) plus standard therapy compared with placebo plus standard therapy. In descriptive subgroup analyses, the PERR and Complete Renal Response (CRR) rates were examined by induction therapy (mycophenolate or cyclophosphamide), biopsy class (Class III or IV, Class III + V or Class IV + V, or Class V), and urine protein:creatinine ratio (uPCR) levels at baseline (<3 g/g or 3 g/g or greater; post-hoc analysis). In descriptive subgroup analyses of time to renal-related event or death, results were consistent with the overall endpoint regardless of induction therapy (mycophenolate or cyclophosphamide), biopsy class (Class III or IV, Class III + V or Class IV + V, or Class V; post-hoc analysis), and baseline proteinuria (<3 g/g or 3 g/g or greater; post-hoc analysis). The treatment differece was primarily driven by the renal worsening and renal-related treatment failure components of the endpoint.

The safety, effectiveness, and pharmacokinetics of belimumab (Benlysta) in children ages 5 to 17 was supported by evidence from adequate and well-controlled studies of belimumab (Benlysta) in the following scenarios: adults with SLE, adults with LN, and pediatric individuals ages 5 to 17 with SLE. The pharmacokinetic data from pediatric individuals was found to be similar to the pharmacokinetic data in adult individuals. It would be expected that the pharmacokinetic exposure would be comparable to adults in pediatric individuals with LN.

OFF-LABEL INDICATIONS

There may be additional indications contained in the Policy section of this document due to evaluation of criteria highlighted in the Company's off-label policy, and/or review of clinical guidelines issued by leading professional organizations and government entities.

References

American Hospital Formulary Service (AHFS). Belimumab (Benlysta®). AHFS Drug Information 2021. [LexiComp Web site]. 03/28/2022. Available at: https://online.lexi.com/lco/action/home [via subscription only]. Accessed August 24, 2022.

Belimumab (Benlysta®) [prescribing information]. Human Genome Sciences, Rockville MD. and GlaxoSmithKline, Research Triangle Park, NC. 07/2022. Available at: https://www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Benlysta/pdf/BENLYSTA-PI-MG.PDF. Accessed August 24, 2022.

Bishton M, Spencer A, Dickinson M, et al. A single-arm, phase II study of the anti-Blys monoclonal antibody belimumab in symptomatic Waldenstrom macroglobulinemia. *Clin Lymphoma Myeloma Leuk*. 2013;13(5):575-578.

Brunner HI, Abud-Mendoza C, Mori M, et al. Efficacy and safety of belimumab in paediatric and adult patients with systemic lupus erythematosus: an across-study comparison. *RMD Open*. 2021;7(3):e001747.

Brunner HI, Abud-Mendoza C, Viola DO, et al. Safety and efficacy of intravenous belimumab in children with systemic lupus erythematosus: results from a randomised, placebo-controlled trial. *Ann Rheum Dis*. 2020;79(10):1340-1348.

Dooley MA, Houssiau F, Aranow C, et al. Effect of belimumab treatment on renal outcomes: results from the phase 3 belimumab clinical trials in patients with SLE. *Lupus*. 2013;22(1):63-72.

Elsevier's Clinical Pharmacology Compendium. Belimumab (Benlysta®). [Clinical Key Web site]. 12/31/2020. Available at: https://www.clinicalkey.com/#!/ [via subscription only]. Accessed August 24, 2022.

Furie R, Robin BH, Houssiau F, et al. Two-year, randomized, controlled trial of belimumab in lupus nephritis. *N Engl J Med*. 2020;383(12):1117-1128.

Furie R, Stohl W, Ginzler EM, et al. Biologic activity and safety of belimumab, a neutralizing anti-B-lymphocyte stimulator (BLyS) monoclonal antibody: a phase I trial in patients with systemic lupus erythematosus. *Arthritis Res Ther*. 2008;10(5):R109.

Ginzler EM, Wallace DJ, Merrill JT, et al. Disease control and safety of belimumab plus standard therapy over 7 years in patients with systemic lupus erythematosus. *J Rheumatol*. 2014;41(2):300-309.

Hanly JG, O'Keeffe AG, Su L, et al. The frequency and outcome of lupus nephritis results from an international inception cohort study. *Rheumatology*. 2016;55:252-262.

IBM Micromedex® DRUGDEX® (electronic version). Belimumab (Benlysta®). [Micromedex Web site]. IBM Watson Health, Greenwood Village, Colorado, USA. 08/19/2022. Available at: https://www.micromedexsolutions.com/micromedex2/librarian [via subscription only]. Accessed August24, 2022.

Lateef A, Petri M. Biologics in the treatment of systemic lupus erythematosus. *Curr Opin Rheumatol*. 2010;22(5):504-509.

Lexi-Drugs Compendium. Belimumab (Benlysta®). [LexiComp Web site]. 08/22/2022. Available at: https://online.lexi.com/lco/action/home [via subscription only]. Accessed August 24, 2022.

Lutalo PM, D'Cruz DP. Update on belimumab for the management of systemic lupus erythematosus. *Expert Opin Biol Ther*. 2014;14(11):1701-1708.

Mariette X, Seror R, Quartuccio L, et al. Efficacy and safety of belimumab in primary Sjögren's syndrome: results of the BELISS open-label phase II study. *Ann Rheum Dis*. 2015;74(3):526-531.

Mok CC, Kwok RC, Yip PS. Effect of renal disease on the standardized mortality ratio and life expectancy of patients with systemic lupus erythematosus. *Arthritis Rheum*. 2013;65(8):2154-2160.

Navarra SV, Guzmán RM, Gallacher AE, et al. Efficacy and safety of belimumab in patients with active systemic lupus erythematosus: a randomized, placebo-controlled, phase 3 trial. *Lancet*. 2011;377(9767):721-731.

Novitas Solutions, Inc. Article (A53127) Self-Administered Drug Exclusion List [Novitas Medicare Services Web site]. Original 10/01/2015. Revised 06/06/2022. Available at: https://www.cms.gov/medicare-coverage-database/view/article.aspx?articleid=53127&ver=111&keyword=belimumab&keywordType=any&areaId=all&docType=NCA,CAL,NCD,MEDCAC,TA,MCD,6,3,5,1,F,P&contractOption=name&contractorName=6&sortBy=relevance&bc=1. Accessed August 24, 2022.

Rovin BH, Furie R, Onno Teng YK, et al. A secondary analysis of the Belimumab International Study in Lupus Nephritis trial examined effects of belimumab on kidney outcomes and preservation of kidney function in patients with lupus nephritis. *Kidney Int.* 2022;101(2):403-413.

Singh JA, Shah NP, Murdano AS. Belimumab for systemic lupus erythematosus. *Cochrane Database Syst Rev*. 2021;2(2):CD010668.

Stohl W, Merrill JT, McKay JD, et al. Efficacy and safety of belimumab in patients with rheumatoid arthritis: a phase II, randomized, double-blind, placebo-controlled, dose-ranging study. *J Rheumatol*. 2013;40(5):579-589.

Thanou-Stavrakil A, Sawalha H. An update on belimumab for the treatment of lupus. *Biologics*. 2011;5:33-43.

Wallace DJ, Navarra S, Petri MA, et al. Safety profile of belimumab: pooled data from placebo-controlled phase 2 and 3 studies in patients with systemic lupus erythematosus. *Lupus*. 2013;22(2):144-154.

US Food and Drug Administration (FDA). Center for Drug Evaluation and Research. Belimumab (Benlysta®). Prescribing information. [FDA web site]. 07/26/2022. Available at: https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed August 24, 2022.

Coding

Inclusion of a code in this table does not imply reimbursement. Eligibility, benefits, limitations, exclusions, precertification/referral requirements, provider contracts, and Company policies apply.

The codes listed below are updated on a regular basis, in accordance with nationally accepted coding guidelines. Therefore, this policy applies to any and all future applicable coding changes, revisions, or updates.

In order to ensure optimal reimbursement, all health care services, devices, and pharmaceuticals should be reported using the billing codes and modifiers that most accurately represent the services rendered, unless otherwise directed by the Company.

The Coding Table lists any CPT, ICD-10, and HCPCS billing codes related only to the specific policy in which they appear.

CPT Procedure Code Number(s)

N/A

ICD - 10 Procedure Code Number(s)

N/A

ICD - 10 Diagnosis Code Number(s)

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

HCPCS Level II Code Number(s)

J0490	Injection, Belimumab 10 mg

Revenue Code Number(s)

N/A

Modifiers

THE FOLLOWING MODIFIER IS USED WHEN REPORTING
Belimumab (Benlysta®) for Intravenous Use

JA	Administered intravenously

Coding And Billing Requirements

For drugs that have more than one method of administration, application of the JA modifier is required to indicate the route of administration.

- To report the intravenous route of administration, append the following modifier: JA Administered Intravenously

Inclusion of a code in this policy does not imply reimbursement. Eligibility, benefits, limitations, exclusions, utilization management/referral requirements, provider contracts, and Company policies apply.

Policy History

Revisions From MA08.057d:

03/28/2025	The policy has been reviewed and reissued to communicate the Company's continuing position on Belimumab (Benlysta®) for intravenous use.
05/07/2024	The policy has been reviewed and reissued to communicate the Company's continuing position on Belimumab (Benlysta®) for intravenous use.
09/05/2023	The policy has been reviewed and reissued to communicate the Company's continuing position on Belimumab (Benlysta®) for intravenous use.
10/24/2022	This version of the policy will become effective 10/24/2022 The following criteria has been **added** to this policy: Coverage for belimumab (Benlysta) in individuals five years of age or older with active systemic lupus erythematosus, with biopsy-proven lupus nephritis Class III, IV, and/or V, have active renal disease at screening, and are receiving concurrent standard treatment for lupus nephritis in accordance with US Food and Drug Administration (FDA) labeling 07/26/2022.

Revisions From MA08.057c:

02/23/2022	The policy has been reviewed and reissued to communicate the Company's continuing position on Belimumab (Benlysta®) for intravenous use.
03/15/2021	This version of the policy will become effective 03/15/2021. The following criteria has been **added** to this policy: Coverage for belimumab (Benlysta) in individuals 18 years of age or older with active systemic lupus erythematosus, with biopsy-proven lupus nephritis Class III, IV, and/or V, have active renal disease at screening, and are receiving concurrent standard treatment for lupus nephritis in accordance with US Food and Drug Administration (FDA) labeling. The policy statement for the use of intravenous cyclophosphamide in combination with belimumab (Benlysta) as experimental/investigational has been removed in accordance with FDA labeling.

Revisions From MA08.057b:

06/08/2020	This version of the policy will become effective 06/08/2020. This policy was updated to include coverage for belimumab (Benlysta®) in pediatric individuals five years of age or older, in accordance with US Food and Drug Administration labeling. Per

	Novitas Solutions, Inc. Article (A53127) For Self-Administered Drug Exclusion List, a Billing Requirement was added to this policy regarding the Coding Modifier: JA Intravenous administration.

Revisions From MA08.057a:

03/27/2019	The policy has been reviewed and reissued to communicate the Company's continuing position on Belimumab (Benlysta®) for intravenous use.
03/28/2018	This policy has been reissued in accordance with the Company's annual review process.
06/07/2017	This policy has been reissued in accordance with the Company's annual review process.
09/28/2016	The policy has been reviewed and reissued to communicate the Company's continuing position on Belimumab (Benlysta®).
11/04/2015	The intent of this policy remains unchanged. The following ICD-10 CM codes have been **added** to this policy: M32.11; M32.12; M32.13; M32.14; M32.15; and M32.19.

Revisions From MA08.057:

01/01/2015	This is a new policy.

Version Effective Date:
10/24/2022
Version Issued Date:
10/24/2022
Version Reissued Date:
03/28/2025