Benlysta® (belimumab) (Intravenous)

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I. Length of Authorization

Coverage will be provided for 12 months and may be renewed.

II. Dosing Limits

A. Quantity Limit (max daily dose) [NDC Unit]:

- Loading Dose (doses administered on days 1, 15 and 29):
  - Benlysta 120 mg single-dose vial for injection: 9 vials per 29 days
  - Benlysta 400 mg single-dose vial for injection: 9 vials per 29 days
- Maintenance Dose:
  - Benlysta 120 mg single-dose vial for injection: 3 vials per 28 days
  - Benlysta 400 mg single-dose vial for injection: 3 vials per 28 days

B. Max Units (per dose and over time) [HCPCS Unit]:

- Loading Dose (doses administered on days 1, 15 and 29):
  - 360 billable units per 29 days
- Maintenance Dose:
  - 120 billable units per 28 days

III. Initial Approval Criteria [1]

- Patient is at least 5 years of age; **AND**

Universal Criteria [1]

- Patient must not have an active infection; **AND**

- Patient will not receive live vaccines during therapy or within 30 days prior to starting treatment; **AND**
- Will not be used in combination with voclosporin; **AND**
- Will not be used in combination with rituximab; **AND**
- Will be used in combination with standard therapy (e.g., anti-malarials, corticosteroids, non-steroidal anti-inflammatory drugs, immunosuppressives); **AND**
- Patient does not have severe active central nervous system lupus; **AND**

Systemic Lupus Erythematosus (SLE) † [1,9,11,12,17]

- Patient has a confirmed diagnosis of SLE with at least 4 diagnostic features (see list of diagnostic SLE criteria below)***** one of which must include a positive autoantibody test (e.g., anti-nuclear antibody [ANA] greater than laboratory reference range and/or anti-double-stranded DNA [anti-dsDNA] greater than 2 fold the laboratory reference range if tested by ELISA); **AND**
- Patient has failed to respond adequately to at least two (2) standard therapies such as anti-malarials, corticosteroids, non-steroidal anti-inflammatory drugs, immunosuppressives (excluding intravenous cyclophosphamide); **AND**
- Patient has one of the following:
  - Safety of Estrogen in Lupus National Assessment – Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) score of 6-12
  - ≥2 British Isles Lupus Assessment Group (BILAG) B organ domain scores

Lupus Nephritis † [1,9,11,12,19]

- Patient has active lupus nephritis Class III, IV, or V as confirmed by renal biopsy; **AND**
- Patient has a confirmed diagnosis of SLE with at least 4 diagnostic features (see list of diagnostic SLE criteria below)***** one of which must include a positive autoantibody test (e.g., anti-nuclear antibody [ANA] greater than laboratory reference range and/or anti-double-stranded DNA [anti-dsDNA] greater than 2 fold the laboratory reference range if tested by ELISA); **AND**
- Patient has failed to respond adequately to standard therapies including corticosteroids AND either cyclophosphamide or mycophenolate mofetil; **AND**
- Baseline measurement of one or more of the following: urine protein:creatinine ratio (uPCR), estimated glomerular filtration rate (eGFR), or urine protein

† FDA Approved Indication(s); **‡** Compendia Recommended Indication(s); **Φ** Orphan Drug

***Systemic Lupus Erythematosus Diagnostic Criteria [11,12]**
Patient must have at least 4 out of 11 diagnostic SLE features: 1. Malar rash 2. Discoid rash 3. Photosensitivity

4. Oral ulcers
5. Nonerosive arthritis (involving 2 or more peripheral joints)
6. Pleuritis/pericarditis
   - Pleuritis - history of pleuritic pain or rubbing heard by a physician or evidence of pleural effusion
   - Pericarditis - documented by electrocardiogram or rubbing heard by a physician or evidence of pericardial effusion
7. Renal disorder
   - Persistent proteinuria > 0.5 grams/day or > 3+ on urine dipstick
   - Cellular casts (red cell, hemoglobin, granular, tubular, or mixed)
8. Seizures/psychosis
9. Hematologic disorder
   - Hemolytic anemia with reticulocytosis
   - Leukopenia < 4,000/mm^3 on ≥ 2 occasions
   - Lymphopenia < 1,500/mm^3 on ≥ 2 occasions
   - Thrombocytopenia < 100,000/mm^3 in the absence of offending drugs
10. Immunologic disorder
    - Presence of anti-Sm or antiphospholipid antibodies
    - Presence of anti-double-stranded DNA [anti-dsDNA] greater than 2 fold the laboratory reference range if tested by ELISA
11. Positive anti-nuclear antibody [ANA] greater than laboratory reference range

IV. Renewal Criteria [1]

Coverage can be renewed based on the following criteria:

- Patient continues to meet universal and other indication-specific relevant criteria such as concomitant therapy requirements (not including prerequisite therapy), performance status, etc. identified in section III; **AND**
- Absence of unacceptable toxicity from the drug. Examples of unacceptable toxicity include: depression, suicidal thoughts, serious infections, signs or symptoms of progressive multifocal leukoencephalopathy (PML), malignancy, severe hypersensitivity reactions/anaphylaxis, serious infusion-related reactions, etc.; **AND**

Systemic Lupus Erythematosus (SLE) [1,9,21]

- Adequate documentation of disease stability and/or improvement as indicated by one or more of the following when compared to pre-treatment baseline:

Improvement in the SELENA-SLEDAI score of ≥4 points; **OR**

- No new BILAG-A organ domain score or 2 new BILAG-B organ domain scores; **OR**
- No worsening (<0.30-point increase) in Physician's Global Assessment (PGA) score; **OR**
- Seroconverted (negative)

Lupus Nephritis [1,19]

- Adequate documentation of disease stability and/or improvement as indicated by one or more of the following when compared to pre-treatment baseline:

Urine protein:creatinine ratio (uPCR); **OR**

- Estimated glomerular filtration rate (eGFR); **OR**
- Urine protein

V. Dosage/Administration [1]

Indication	Dose
Systemic Lupus Erythematosus (SLE) or Lupus Nephritis	• Loading Dose: 10 mg/kg intravenously (by a healthcare provider) every 2 weeks x 3 doses (days 1, 15 and 29) • Maintenance Dose: 10 mg/kg intravenously (by a healthcare provider) every 4 weeks

VI. Billing Code/Availability Information

HCPCS Code:

- J0490 – Injection, belimumab, 10 mg; 1 billable unit = 10 mg

NDC:

- Benlysta 120 mg/5 mL single-dose vial for injection: 49401-0101-xx
- Benlysta 400 mg/20 mL single-dose vial for injection: 49401-0102-xx

VII. References

1. Benlysta [package insert]. Philadelphia, PA; GlaxoSmithKline LLC; February 2023. Accessed March 2023.
2. Boyce EG, Fusco BE. Belimumab: review of use in systemic lupus erythematosus. Clin Ther. 2012 May;34(5):1006-22. doi: 10.1016/j.clinthera.2012.02.028. Epub 2012 Mar 30.
3. Navarra SV, Guzmán RM, Gallacher AE, et al. Efficacy and safety of belimumab in patients with active systemic lupus erythematosus: a randomised, placebo-controlled, phase 3 trial. Lancet. 2011 Feb;377(9767):721-31. doi: 10.1016/SO140-6736(10)61354-2. Epub 2011 Feb 4.
4. Furie R, Petri M, Zamani O, et al. A phase III, randomized, placebo-controlled study of belimumab, a monoclonal antibody that inhibits B lymphocyte stimulator, in patients with systemic lupus erythematosus. Arthritis Rheum. 2011 Dec;63(12):3918-30. doi: 10.1002/art.30613.
5. Petri M, Orbai AM, Alarcón GS, et al. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. Arthritis Rheum. 2012 Aug;64(8):2677-86. doi: 10.1002/art.34473.

6. 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. doi: 10.1186/ar2506. Epub 2008 Sep 11.
7. Kim SS, Kirou KA, Erkan D. Belimumab in systemic lupus erythematosus: an update for clinicians. Ther Adv Chronic Dis. 2012 Jan;3(1):11-23. doi: 10.1177/2040622311424806.
8. Calvo-Alén J1, Silva-Fernández L, Úcar-Angulo E, et al. SER consensus statement on the use of biologic therapy for systemic lupus erythematosus. Reumatol Clin. 2013 Sep-Oct;9(5):281-96.
9. Gordon C, Amissah-Arthur MB, Gayed M, et al. The British Society for Rheumatology guideline for the management of systemic lupus erythematosus in adults. Rheumatology (Oxford). 2018 Jan 1;57(1):e1-e45. doi: 10.1093/rheumatology/kex286.
10. NICE. Belimumab for treating active autoantibody-positive systemic lupus erythematosus: Technology Appraisal Guidance [TAG397]. https://www.nice.org.uk/guidance/ta397. Published: 22 June 2016. Accessed March 2021.
11. American College of Rheumatology Ad Hoc Committee on Systemic Lupus Erythematosus Guidelines. Guidelines for referral and management of systemic lupus erythematosus in adults. Arthritis Rheum. 1999;42(9):1785–1796.
12. Lam NC, Ghetu MV, Bieniek ML. Systemic Lupus Erythematosus: Primary Care Approach to Diagnosis and Management. Am Fam Physician. 2016 Aug 15;94(4):284-94.
13. Wallace DJ, Stohl W, Furie RA, et al. A Phase II, Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Study of Belimumab in Patients With Active Systemic Lupus Erythematosus. Arthritis Rheum, 61 (9), 1168-78, 2009 Sept 15. doi: 10.1002/art.24699
14. D'Cruz D, Maksimowicz-McKinnon K, Oates J, et al. Efficacy and safety of belimumab in patients of black race with systemic lupus erythematosus: results from the EMBRACE study. 10.1136/lupus-2019-lsm.199
15. Brunner HI, Abud-Mendoza C, Viola DI, et al. Efficacy and Safety of Intravenous Belimumab in Children with Systemic Lupus Erythematosus [abstract]. *Arthritis Rheumatol.* 2018; 70 (suppl 10). https://acrabstracts.org/abstract/efficacy-and-safety-of-intravenous-belimumab-in-children-with-systemic-lupus-erythematosus/
16. Stohl W, Schwarting A, Okada M, et al. Efficacy and Safety of Subcutaneous Belimumab in Systemic Lupus Erythematosus: A Fifty-Two-Week Randomized, Double-Blind, Placebo-Controlled Study. Arthritis Rheumatol, 69 (5), 1016-1027; May 2017. DOI: 10.1002/art.40049.
17. Fanouriakis A, Kostopoulou M, Alunno A, et al. 2019 update of the EULAR recommendations for the management of systemic lupus erythematosus. Ann Rheum Dis 2019;78: 736–745.
18. Furie R, Rovin BH, Houssiau F, et al. Two-Year, Randomized, Controlled Trial of Belimumab in Lupus Nephritis. N Engl J Med 2020; 383:1117-1128. DOI: 10.1056/NEJMoa2001180.

19. Hahn BH, McMahon MA, Wilkinson A, et al. American College of Rheumatology guidelines for screening, treatment, and management of lupus nephritis. Arthritis Care Res (Hoboken). 2012;64(6):797-808. doi:10.1002/acr.21664.
20. Bertsias GK, Tektonidou M, Amoura Z, et al. Joint European League Against Rheumatism and European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of adult and paediatric lupus nephritis. Ann Rheum Dis. 2012;71(11):1771-1782. doi:10.1136/annrheumdis-2012-201940.
21. NICE. Belimumab for treating active autoantibody-positive systemic lupus erythematosus: Technology appraisal guidance [TA752]. https://www.nice.org.uk/guidance/ta752. Published: 15 December 2021. Accessed March 2023.

Appendix 1 – Covered Diagnosis Codes

ICD-10	ICD-10 Description
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

Appendix 2 – Centers for Medicare and Medicaid Services (CMS)

Medicare coverage for outpatient (Part B) drugs is outlined in the Medicare Benefit Policy Manual (Pub. 100-2), Chapter 15, §50 Drugs and Biologicals. In addition, National Coverage Determination (NCD), Local Coverage Determinations (LCDs), and Local Coverage Articles (LCAs) may exist and compliance with these policies is required where applicable. They can be found at: https://www.cms.gov/medicare-coverage-database/search.aspx. Additional indications may be covered at the discretion of the health plan.

Medicare Part B Covered Diagnosis Codes (applicable to existing NCD/LCD/LCA): N/A

Medicare Part B Administrative Contractor (MAC) Jurisdictions		
Jurisdiction	**Applicable State/US Territory**	**Contractor**
E (1)	CA, HI, NV, AS, GU, CNMI	Noridian Healthcare Solutions, LLC

Medicare Part B Administrative Contractor (MAC) Jurisdictions		
Jurisdiction	**Applicable State/US Territory**	**Contractor**
F (2 & 3)	AK, WA, OR, ID, ND, SD, MT, WY, UT, AZ	Noridian Healthcare Solutions, LLC
5	KS, NE, IA, MO	Wisconsin Physicians Service Insurance Corp (WPS)
6	MN, WI, IL	National Government Services, Inc. (NGS)
H (4 & 7)	LA, AR, MS, TX, OK, CO, NM	Novitas Solutions, Inc.
8	MI, IN	Wisconsin Physicians Service Insurance Corp (WPS)
N (9)	FL, PR, VI	First Coast Service Options, Inc.
J (10)	TN, GA, AL	Palmetto GBA, LLC
M (11)	NC, SC, WV, VA (excluding below)	Palmetto GBA, LLC
L (12)	DE, MD, PA, NJ, DC (includes Arlington & Fairfax counties and the city of Alexandria in VA)	Novitas Solutions, Inc.
K (13 & 14)	NY, CT, MA, RI, VT, ME, NH	National Government Services, Inc. (NGS)
15	KY, OH	CGS Administrators, LLC