Drug Coverage Policy

Effective Date.....09/01/2024
Coverage Policy Number.....IP0429
Policy Title.....Benlysta Intravenous

Lupus – Benlysta Intravenous

- Benlysta® (belimumab intravenous infusion – GlaxoSmithKline)

INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment and have discretion in making individual coverage determinations. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Cigna Healthcare Coverage Policy

OVERVIEW
Benlysta intravenous, a B-lymphocyte stimulator (BLyS)-specific inhibitor, is indicated for the following uses:[1]

- **Lupus nephritis**, in patients ≥ 5 years of age with active disease who are receiving standard therapy.
- **Systemic lupus erythematosus** (SLE), in patients ≥ 5 years of age with active disease who are receiving standard therapy.

Benlysta has not been studied and is not recommended in patients with severe active central nervous system lupus.[1] The efficacy of Benlysta for the treatment of SLE was studied in patients with a history of autoantibodies (anti-nuclear antibody and/or anti-double-stranded DNA) and an

exploratory analysis of the pivotal trial indicated Benlysta was beneficial in patients who were autoantibody positive.

Guidelines
Guidelines for the management of lupus nephritis from Kidney Disease: Improving Global Outcomes (KDIGO) [2024] recommendations include Benlysta or Lupkynis in combination with other medications plus glucocorticoids as initial treatment options for patients with active Class III or IV biopsy confirmed lupus nephritis (strong recommendation, moderate certainty of evidence).[3] No preference is given between the treatment protocol options; however, the KDIGO guidelines do provide individual patient clinical factors to consider, including but not limited to, kidney function and histology, risk of disease flare, proteinuria, background suppression, and need for parenteral therapy.

European League Against Rheumatism (EULAR) guidelines for SLE (2023 update) recommend hydroxychloroquine for all patients, unless contraindicated.[2] Depending on the type and severity of organ involvement, glucocorticoids can be used but dosing should be minimized or withdrawn when possible. Methotrexate, azathioprine, mycophenolate, and/or biologic agents (Benlysta, Saphnelo® [anifrolumab-fnia intravenous infusion]) should be considered in patients who do not respond to hydroxychloroquine ± glucocorticoids. EULAR also states biologic agents (Benlysta, Saphnelo) should be considered as second-line therapy for the treatment of patients with active skin disease. Patient with active proliferative lupus nephritis should also consider combination therapy with biologic agents (Benlysta, Lupkynis™ [voclosporin capsules]). In general, the pharmacological interventions should be directed by patient specific characteristics and the type/severity of organ involvement.

Medical Necessity Criteria

Benlysta intravenous is considered medically necessary when the following criteria are met:

FDA-Approved Indications

1. **Lupus Nephritis.** Approve for the duration noted if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, iii, and iv):
     - **i.** Patient is ≥ 5 years of age; AND
     - **ii.** Diagnosis of lupus nephritis has been confirmed on biopsy; AND
       Note: For example, World Health Organization class III, IV, or V lupus nephritis.
     - **iii.** The medication is being used concurrently with an immunosuppressive regimen; AND
       Note: Examples of an immunosuppressive regimen include azathioprine, cyclophosphamide, leflunomide, methotrexate, mycophenolate mofetil, and/or a systemic corticosteroid.
     - **iv.** The medication is prescribed by or in consultation with a nephrologist or rheumatologist.
   - **B)** Patient is Currently Receiving Benlysta Intravenous or Subcutaneous. Approve for 1 year if the patient meets ALL of the following (i, ii, and iii):
     - **i.** The medication is being used concurrently with an immunosuppressive regimen; AND
       Note: Examples of an immunosuppressive regimen include azathioprine, cyclophosphamide, leflunomide, methotrexate, mycophenolate mofetil, and/or a systemic corticosteroid.
     - **ii.** The medication is prescribed by or in consultation with a nephrologist or rheumatologist; AND

iii. Patient has responded to Benlysta subcutaneous or intravenous, as determined by the prescriber.
Note: Examples of a response include improvement in organ dysfunction, reduction in flares, reduction in corticosteroid dose, decrease of anti-dsDNA titer, and improvement in complement levels (i.e., C3, C4).

Dosing. Approve the following dosing regimen (A and B):
A) The dose is up to 10 mg/kg given as an intravenous infusion; AND
B) Doses are administered at Weeks 0, 2, and 4, with subsequent doses separated by at least 4 weeks.

2. Systemic Lupus Erythematosus (SLE). Approve for the duration noted if the patient meets ONE of the following (A or B):
A) Initial Therapy. Approve for 4 months if the patient meets ALL of the following (i, ii, iii, and iv):
i. Patient is ≥ 5 years of age; AND
ii. Patient has autoantibody-positive systemic lupus erythematosus (SLE), defined as positive for antinuclear antibodies (ANA) and/or anti-double-stranded DNA (anti-dsDNA) antibody; AND
Note: Not all patients with SLE are positive for anti-dsDNA, but most will be positive for ANA.
iii. Patient meets ONE of the following (a or b):
a) The medication is being used concurrently with at least one other standard therapy; OR
Note: Examples of standard therapies include an antimalarial (e.g., hydroxychloroquine), systemic corticosteroid (e.g., prednisone), and other immunosuppressants (e.g., azathioprine, mycophenolate mofetil, methotrexate).
b) Patient is determined to be intolerant to standard therapy due to a significant toxicity, as determined by the prescriber; AND
iv. The medication is prescribed by or in consultation with a rheumatologist, clinical immunologist, nephrologist, neurologist, or dermatologist.
B) Patient is Currently Receiving Benlysta Intravenous or Subcutaneous. Approve for 1 year if the patient meets ALL of the following (i, ii, and iii):
i. Patient meets ONE of the following (a or b):
a) The medication is being used concurrently with at least one other standard therapy; OR
Note: Examples of standard therapies include an antimalarial (e.g., hydroxychloroquine), systemic corticosteroid (e.g., prednisone), and other immunosuppressants (e.g., azathioprine, mycophenolate mofetil, methotrexate).
b) Patient is determined to be intolerant to standard therapy due to a significant toxicity, as determined by the prescriber; AND
ii. The medication is prescribed by or in consultation with a rheumatologist, clinical immunologist, nephrologist, neurologist, or dermatologist; AND
iii. Patient has responded to Benlysta subcutaneous or intravenous, as determined by the prescriber.
Note: Examples of a response include reduction in flares, reduction in corticosteroid dose, decrease of anti-dsDNA titer, improvement in complement levels (i.e., C3, C4), or improvement in specific organ dysfunction (e.g., musculoskeletal, blood, hematologic, vascular, others).

Dosing. Approve the following dosing regimen (A and B):
A) The dose is up to 10 mg/kg given as an intravenous infusion; AND

B) Doses are administered at Weeks 0, 2, and 4, with subsequent doses separated by at least 4 weeks.

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Receipt of sample product does not satisfy any criteria requirements for coverage.

Conditions Not Covered

Any other use is considered experimental, investigational, or unproven, including the following (this list may not be all inclusive; criteria will be updated as new published data are available):

1. **Concurrent Use with Other Biologics.** Benlysta intravenous has not been studied and is not recommended in combination with other biologics.[1] Safety and efficacy have not been established with these combinations. See APPENDIX for examples of other biologics that should not be taken in combination with Benlysta.

2. **Concurrent Use with Lupkynis (voclosporin capsules).** Lupkynis has not been studied in combination with biologics such as Benlysta.[1]

3. **Rheumatoid Arthritis.** A Phase II dose-ranging study evaluating patients with rheumatoid arthritis showed only small American College of Rheumatology (ACR) 20 responses with Benlysta (e.g., ACR 20 response at Week 24 was 28% with Benlysta 10 mg/kg).[4] Numerous other agents are available with higher ACR responses and established efficacy for RA.

References

1. Benlysta® injection [prescribing information]. Durham, NC: GlaxoSmithKline; May 2024.
2. Fanouriakis A, Kostopoulou M, Andersen J, et al. EULAR recommendations for the management of systemic lupus erythematosus: 2023 update. *Ann Rheum Dis*. 2024;83(1):15-29.
3. Kidney Disease: Improving Global Outcomes (KDIGO) Lupus Nephritis Work Group. KDIGO 2024 Clinical Practice Guideline for the management of LUPUS NEPHRITIS. *Kidney Int.* 2024;105(1S):S1-S69.
4. 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.

Revision Details

Type of Revision	Summary of Changes	Date
Annual Revision	**Policy Name Change: Updated** Policy Name from "Belimumab Intravenous" to "Lupus – Benlysta Intravenous." **Lupus Nephritis: Updated** the requirement that the patient is taking with standard therapy to more generally require that the patient is taking an immunosuppressive regimen. **Removed** the	09/01/2024

	exception for a patient who is intolerant to standard therapy due to significant toxicity as determined by the prescriber. **Updated** initial therapy duration to 6 months from 12 months. **Systemic Lupus Erythematosus**: **Updated** initial therapy duration to 4 months from 12 months. **Conditions Not Covered: Removed** severe active central nervous system lupus.	

The policy effective date is in force until updated or retired.

APPENDIX

	Mechanism of Action	Examples of Inflammatory Indications*
Biologics		
Benlysta® (belimumab SC injection, IV infusion)	BLyS inhibitor	SLE, lupus nephritis
Saphnelo™ (anifrolumab-fnia IV infusion)	IFN receptor antagonist	SLE
Adalimumab SC Products (Humira®, biosimilars)	Inhibition of TNF	AS, CD, JIA, PsO, PsA, RA, UC
Cimzia® (certolizumab pegol SC injection)	Inhibition of TNF	AS, CD, nr-axSpA, PsO, PsA, RA
Etanercept SC Products (Enbrel®, biosimilars)	Inhibition of TNF	AS, JIA, PsO, PsA
Infliximab IV Products (Remicade®, biosimilars)	Inhibition of TNF	AS, CD, PsO, PsA, RA, UC
Simponi®, Simponi® Aria™ (golimumab SC injection, golimumab IV infusion)	Inhibition of TNF	SC formulation: AS, PsA, RA, UC
		IV formulation: AS, PJIA, PsA, RA
Actemra® (tocilizumab IV infusion, tocilizumab SC injection)	Inhibition of IL-6	SC formulation: PJIA, RA, SJIA
		IV formulation: PJIA, RA, SJIA
Kevzara® (sarilumab SC injection)	Inhibition of IL-6	RA
Orencia® (abatacept IV infusion, abatacept SC injection)	T-cell costimulation modulator	SC formulation: JIA, PsA, RA
		IV formulation: JIA, PsA, RA
Rituximab IV Products (Rituxan®, biosimilars)	CD20-directed cytolytic antibody	RA
Kineret® (anakinra SC injection)	Inhibition of IL-1	JIA^, RA
Stelara® (ustekinumab SC injection, ustekinumab IV infusion)	Inhibition of IL-12/23	SC formulation: CD, PsO, PsA, UC
		IV formulation: CD, UC
Siliq™ (brodalumab SC injection)	Inhibition of IL-17	PsO
Cosentyx® (secukinumab SC injection)	Inhibition of IL-17A	AS, ERA, nr-axSpA, PsO, PsA
Taltz® (ixekizumab SC injection)	Inhibition of IL-17A	AS, nr-axSpA, PsO, PsA
Ilumya™ (tildrakizumab-asmn SC injection)	Inhibition of IL-23	PsO
Skyrizi® (risankizumab-rzaa SC injection)	Inhibition of IL-23	PsA, PsO
Tremfya™ (guselkumab SC injection)	Inhibition of IL-23	PsO
Entyvio™ (vedolizumab IV infusion)	Integrin receptor antagonist	CD, UC

* Not an all-inclusive list of indication (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; IV – Intravenous; BLyS – B-lymphocyte stimulator-specific inhibitor; SLE – Systemic lupus erythematosus; IFN – Interferon; TNF – Tumor necrosis factor; AS – Ankylosing spondylitis; CD – Crohn's disease; JIA – Juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; UC – Ulcerative colitis; nr-axSpA – Non-radiographic axial spondyloarthritis; PJIA – Polyarticular juvenile idiopathic arthritis; IL – Interleukin; SJIA – Systemic juvenile idiopathic arthritis; ^ Off-label use of Kineret in JIA supported in guidelines; ERA – Enthesitis-related arthritis.