POLICY: Inflammatory Conditions – Benlysta® (belimumab intravenous injection – Human Genome Sciences, Inc./GlaxoSmithKline)

DATE REVIEWED: 05/27/2020

OVERVIEW

Benlysta intravenous is a B-lymphocyte stimulator (BLyS)-specific inhibitor.[1] It is indicated for the treatment of active, autoantibody-positive, systemic lupus erythematosus (SLE) in patients ≥ 5 years of age who are receiving standard therapy. Benlysta intravenous has not been studied and is not recommended in those with severe active lupus nephritis, severe active central nervous system (CNS) lupus, or in combination with other biologics or intravenous (IV) cyclophosphamide. In some of the clinical trials involving Benlysta, Black patients had a lower response rate for the primary endpoint relative to Black patients receiving placebo; therefore, caution is recommended when considering Benlysta in Black patients. Of note, there is also a subcutaneous formulation of Benlysta with a similar indication except use is limited to adults ≥ 18 years.

Guidelines

Guidelines from the European League Against Rheumatism (EULAR) [2019] recommend consideration of add-on therapy with Benlysta for patients who have an inadequate response to standard of care (e.g., combinations of hydroxychloroquine and glucocorticoids with or without immunosuppressive agents).[2] EULAR defines an inadequate response as residual disease activity not allowing tapering of glucocorticoids and/or frequent relapses. Guidelines for lupus nephritis from the American College of Rheumatology (ACR) [2012] do not address Benlysta's place in therapy.[3]

POLICY STATEMENT

Prior authorization is recommended for medical benefit coverage of Benlysta intravenous. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication(s). Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Because of the of the specialized skills required for evaluation and diagnosis of patients treated with Benlysta IV as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Benlytsta IV to be prescribed by or in consultation with a physician who specializes in the condition being treated.

RECOMMENDED AUTHORIZATION CRITERIA

FDA-Approved Indications

1. **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 conditions (i, ii, iii, and iv):
     - **i.** The patient is ≥ 5 years of age; AND

ii. The patient has autoantibody-positive 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. The patient meets ONE of the following (a or b):

a) The agent 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) The patient is determined to be intolerant to standard therapy due to a significant toxicity, as determined by the prescriber; AND

iv. The agent is prescribed by or in consultation with 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 criteria (i, ii, and iii):

i. The patient meets ONE of the following (a or b):

a) The agent 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) The patient is determined to be intolerant to standard therapy due to a significant toxicity, as determined by the prescriber; AND

ii. The agent is prescribed by or in consultation with rheumatologist, clinical immunologist, nephrologist, neurologist, or dermatologist; AND

iii. The 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 (A and B):

A) The dose is up to 10 mg/kg given as an IV infusion; AND

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

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Benlysta Intravenous has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

1. **Concurrent Use with Other Biologics or with Cyclophosphamide Intravenous (IV).** Benlysta IV has not been studied and is not recommended in combination with other biologics or IV cyclophosphamide in patients with SLE.[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. **Rheumatoid Arthritis (RA).** A Phase II dose-ranging study evaluating patients with RA showed only small ACR 20 responses with Benlysta (e.g., American College of Rheumatology [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.

3. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Benlysta® injection [prescribing information]. Rockville, MD: Human Genmome Science Inc./GlaxoSmithKline; January 2020.
2. 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(6):736-745..
3. 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.
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.

HISTORY

Type of Revision	Summary of Changes	Date Reviewed
New Policy	--	07/18/2018
Early annual revision	**Systemic Lupus Erythematosus:** To align with the new pediatric indication, criteria for initial therapy were changed to approve in patients ≥ 5 years of age (previously was ≥ 18 years of age). For patients continuing therapy, remove the criterion that requires a patient to be ≥ 18 years of age.	05/09/2019
Annual revision	**Systemic Lupus Erythematosus:** Clarify in criteria that autoantibody-positive SLE is defined as patients who are positive for antinuclear antibodies (ANA) and/or anti-double-stranded DNA antibody (previously this was listed as an i.e. in the criteria). Examples standard therapies were moved to a Note in the criteria section (previously listed within the criteria). For the exceptions applying to patients with an intolerance to standard therapy, wording was updated to more generally allow this determination by the prescriber (criteria previously specified this was according to the prescribing physician). Examples of a response to therapy were moved to a note (previously included within the criteria). In the dosing section, the approval was adjusted to allow for approval of up to the weight-based dose (previously required dose to be the listed weight-based dose). Doing was also updated to require at least 4 weeks separating subsequent maintenance doses (previously criteria specifically required 4 weeks between all subsequent doses but was not worded to allow for dose delays).	05/27/2020

APPENDIX

	Mechanism of Action	Examples of Inflammatory Indications for Products*
Biologics		
Adalimumab SC Products (Humira®, biosimilars)	Inhibition of TNF	AS, CD, PJIA, PsO, PsA, RA, SJIA, UC
Cimzia® (certolizumab pegol SC injection)	Inhibition of TNF	AS, CD, PsO, PsA, RA
Etanercept SC Products (Enbrel®, biosimilars)	Inhibition of TNF	AS, PJIA, PsO, PsA, RA, SJIA
Infliximab IV Products (Remicade®, biosimilars)	Inhibition of TNF	AS, CD, PJIA, PsO, PsA, RA, SJIA, UC
Simponi®, Simponi® Aria™ (golimumab SC injection, golimumab IV infusion)	Inhibition of TNF	SC formulation: AS, PsA, RA, UC
		IV formulation: AS, 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: PJIA, PSA, RA
		IV formulation: PJIA, PsA, RA
Rituximab IV Products (Rituxan®, biosimilars)	CD20-directed cytolytic antibody	RA
Ilaris (canakinumab SC injection**)**	Inhibition of IL-1β	SJIA
Kineret® (anakinra SC injection)	Inhibition of IL-1	RA, SJIA^
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, PsO, PsA
Taltz® (ixekizumab SC injection)	Inhibition of IL-17A	AS, PsO, PsA
Ilumya™ (tildrakizumab-asmn SC injection)	Inhibition of IL-23	PsO
Skyrizi™ (risankizumab-rzza SC injection)	Inhibition of IL-23	PsO
Tremfya™ (guselkumab SC injection)	Inhibition of IL-23	PsO
Entyvio™ (vedolizumab IV infusion)	Integrin receptor antagonist	CD, UC
Targeted Synthetic DMARDs		
Otezla® (apremilast tablets)	Inhibition of PDE4	PsO, PsA
Olumiant® (baricitinib tablets)	Inhibition of the JAK pathways	RA
Rinvoq® (upadacitinib extended-release tablets)	Inhibition of the JAK pathways	RA
Xeljanz®, Xeljanz XR (tofacitinib tablets, tofacitinib extended-release tablets)	Inhibition of the JAK pathways	RA, PsA, 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; TNF – Tumor necrosis factor; IV – Intravenous, IL – Interleukin; PDE4 – Phosphodiesterase 4; JAK – Janus kinase; AS – Ankylosing spondylitis; CD – Crohn's disease; PJIA – Polyarticular juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; SJIA – Systemic juvenile idiopathic arthritis; UC – Ulcerative colitis; ^ Off-label use of SJIA supported in guidelines.