Clinical Policy: Belimumab (Benlysta)

Reference Number: ERX.SPA.213
Effective Date: 12.01.15
Last Review Date: 05.21
Line of Business: Commercial, Medicaid

Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description
Belimumab (Benlysta®) is B-lymphocyte stimulator specific inhibitor.

FDA Approved Indication(s)
Benlysta is indicated for the treatment of:
- Patients aged 5 years and older with active, autoantibody-positive, systemic lupus erythematosus (SLE) who are receiving standard therapy
- Adult patients with active lupus nephritis (LN) who are receiving standard therapy

Limitation(s) of use: The efficacy of Benlysta has not been evaluated in patients with severe active lupus nephritis or severe active central nervous system lupus. Benlysta has not been studied in combination with other biologics or intravenous cyclophosphamide. Use of Benlysta is not recommended in these situations.

Policy/Criteria
Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.

It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ that Benlysta is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Systemic Lupus Erythematosus (must meet all)**:**
1. Diagnosis of SLE;
2. Prescribed by or in consultation with a rheumatologist;
3. Age ≥ 5 years;
4. Documentation confirms that member is positive for an SLE autoantibody (e.g., anti-nuclear antibody (ANA), anti-double-stranded DNA (anti-dsDNA), anti-Smith (anti-Sm), anti-ribonucleoprotein (anti-RNP), anti-Ro/SSA, anti-La/SSB, antiphospholipid antibody);
5. Prescribed in combination with standard therapy for SLE that includes one or more of the following agents, unless all agents are contraindicated: glucocorticoids (e.g., prednisone), antimalarial (e.g., hydroxychloroquine or chloroquine), non-biologic immunosuppressants (e.g., azathioprine, methotrexate, mycophenolate);
6. Request meets one of the following (a or b):
   a. Adults (≥ 18 years of age):
      i. IV: Dose does not exceed 10 mg/kg per dose at 2-week intervals for the first 3 doses and at 4-week intervals thereafter;
      ii. SC: 200 mg per week;
   b. Pediatrics (≥ 5 years of age): Dose does not exceed 10 mg/kg per dose IV at 2-week intervals for the first 3 doses and at 4-week intervals thereafter.

Approval duration: 6 months

B. Lupus Nephritis (must meet all)**:**
1. Diagnosis of LN with kidney biopsy that confirms one of the following (a, b, or c):
   a. LN Class III (focal);
   b. LN Class IV (diffuse segmental or global);
   c. LN Class V (membranous);
2. Prescribed by or in consultation with a nephrologist or rheumatologist;
3. Age ≥ 18 years;
4. Member has a confirmed diagnosis of SLE;
5. Prescribed in combination with standard therapy for SLE that includes one or more of the following agents, unless all agents are contraindicated: glucocorticoids (e.g., prednisone), antimalarial (e.g., hydroxychloroquine or chloroquine), non-biologic immunosuppressants (e.g., azathioprine, cyclophosphamide, methotrexate, mycophenolate);
6. Request meets one of the following (a or b):
   a. IV: Dose does not exceed 10 mg/kg per dose at 2-week intervals for the first 3 doses and at 4-week intervals thereafter;
   b. SC: Dose does not exceed 400 mg per week SC for the first 4 doses*, then 200 mg per week SC.

   **Loading doses not permitted if previously receiving Benlysta for treatment of SLE*

Approval duration: 6 months

C. Other diagnoses/indications
1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Therapy

A. All Indications in Section I (must meet all)**:**
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
2. Member meets one of the following (a or b):
   a. For SLE: Member is responding positively to therapy;
   b. For LN: Member is responding positively to therapy as evidenced by one of the following (i, ii, or iii):
      i. Reduced level of proteinuria measured by UPCR ≤ 0.5 mg/mg from baseline with low dose steroids (e.g., prednisone);
      ii. No reduction from baseline in eGFR of greater than 20% with low dose steroids (e.g., prednisone);
      iii. eGFR ≥ 60 mL/min/1.73 m^2 with low dose steroids (e.g., prednisone);
3. Prescribed in combination with standard therapy for SLE that includes one or more of the following agents, unless all agents are contraindicated: glucocorticoids (e.g., prednisone), antimalarial (e.g., hydroxychloroquine or chloroquine), non-biologic immunosuppressants (e.g., azathioprine, methotrexate, mycophenolate);
4. If request is for a dose increase, request meets one of the following (a or b):
   a. Adults (≥ 18 years of age):
      i. IV: Dose does not exceed 10 mg/kg per dose at 2-week intervals for the first 3 doses and at 4-week intervals thereafter;
      ii. SC: 200 mg per week;
   b. Pediatrics (≥ 5 years of age): Dose does not exceed 10 mg/kg per dose IV at 2-week intervals for the first 3 doses and at 4-week intervals thereafter.

Approval duration: 12 months

B. Other diagnoses/indications (must meet 1 or 2)**:**
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions and documentation supports positive response to therapy.
   Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off-label use policy – ERX.PA.01 or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

ANA: anti-nuclear antibody
Anti-dsDNA: anti-double-stranded DNA
Anti-Sm: anti-Smith
DNA: deoxyribonucleic acid
FDA: Food and Drug Administration
SLE: systemic lupus erythematosus

Appendix B: Therapeutic Alternatives

This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent for all relevant lines of business and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
glucocorticoids (e.g., prednisone)	Varies	Varies
antimalarial agents (e.g., hydroxychloroquine, chloroquine)	Varies	Varies
non-biologic immunosuppressants (e.g., azathioprine, methotrexate, mycophenolate)*	Varies	Varies

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.
** For LN, cyclophosphamide is also an acceptable immunosuppressant.*

Appendix C: Contraindications/Boxed Warnings

- Contraindication(s): previous anaphylaxis to belimumab
- Boxed warning(s): none reported

Appendix D: Autoantibody Positive Versus Negative SLE

Only one of the five Benlysta pivotal trials included patients with autoantibody negative SLE; no significant differences between any of the Benlysta groups and the placebo group were observed. However, on further analysis Benlysta appeared to offer benefit to a subgroup of autoantibody positive patients. Benlysta's efficacy was confirmed in the remaining four trials which included only autoantibody positive patients. Because of the apparent lack of efficacy in autoantibody negative patients and because the FDA has approved Benlysta in only autoantibody positive patients, Benlysta coverage will not be authorized for patients with autoantibody negative SLE.

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose

SLE, LN	• IV (pediatrics and adults
	  ○ 10 mg/kg at 2 week intervals for the first 3 doses and at 4 week intervals thereafter (pediatrics and adults)
	• SC (adults only)
	  ○ For SLE, 200 mg once weekly
	  ○ For lupus nephritis, 400 mg once weekly for 4 doses, then 200 mg once weekly
	• Transition from IV to SC therapy (adults)
	  ○ May transition from IV to SC therapy any time after the first 2 IV doses; Administer first SC dose 1 to 2 weeks after the last IV dose
		IV: 10 mg/kg/dose
		SC: 200 mg/week

VI. Product Availability

- Single-dose vial: 120 mg and 400 mg lyophilized powder for reconstitution
- Single-dose prefilled autoinjector/syringe: 200 mg/mL

VII. References

1. Benlysta Prescribing Information. Research Triangle Park, NC: GlaxoSmithKline; March 2021. Available at http://www.benlysta.com. Accessed July 22, 2021.
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;0:1–10. doi:10.1136/annrheumdis-2019-215089.
3. 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; 64:2677.
4. 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*. 2018;57:e1-e45. doi:10.1093/rheumatology/kex286.
5. Furie R, Rovin B, Houssiau F, et al. Two-year randomized, controlled trial of belimumab in lupus nephritis. *N Engl J Med.* 2020;3838(12):1117-1128. doi:10.1056/NEJMoa2001180.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
4Q 2017 Annual Review: No significant changes. References updated and added age per PI.	09.17.17	11.17
3Q 2018 annual review: no significant changes; expanded list of accepted autoantibodies; references reviewed and updated.	05.09.18	08.18
3Q 2019 annual review: no significant changes; labeled age updated from adults down to age 5 and older; antiphospholipid antibody added to examples of SLE antibodies; added that concurrent standard therapy be continued in the continued approval section; references reviewed and updated.	05.14.19	08.19
3Q 2020 annual review: no significant changes; references reviewed and updated.	05.12.20	08.20
RT4: added criteria to reflect new indication for lupus nephritis in adults and aligned with Lupkynis (voclosporin).	02.16.21	05.21
Added IV dosing option for LN per FDA labeling.	06.08.21	
Added cyclosphosphamide as allowed standard of care treatment for LN; clarified dosing for transitioning from IV to SC.	07.22.21	

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members.