Benlysta (belimumab)

- Benlysta (belimumab) [120mg, 400mg] Powder for Injection
- Benlysta (belimumab) SC 200 mg/mL Autoinjector Solution for Injection
- Benlysta (belimumab) SC 200 mg/mL Prefilled Syringe Solution for Injection

Summary

Systemic lupus erythematosus (SLE) is an autoimmune disease that can impact almost every organ in the body. Common symptoms include fatigue, fever and weight loss, and many will experience joint pain (arthralgias and arthritis), skin lesions, and cardiac, kidney, lung, and gastrointestinal disease, anemia and neurological side effects (cognitive impairment, psychosis, seizures, headaches or neuropathies). It is characterized by periods of remissions and relapses. The first line of therapy for anyone ith SLE includes hydroxychloroquine with or without a steroid depending on disease severity. Other therapies include azathioprine, methotrexate, mycophenolate, Saphnelo (anifrolumab), rituximab (Rituxan), and Benlysta (belimumab).

Lupus nephritis can occur in those with SLE with kidney involvement. Lupus nephritis (LN) typically occurs early in the disease course and is diagnosed by an abnormal urinalysis (including elevated protein in the urine, microscopic hematuria). Management of LN includes preventative management by treating SLE with hydroxychloroquine, supportive care through dietary modifications (low sodium and protein restrictions) and blood pressure control. Immunosuppression should be used in those with focal or diffuse LN who have active lesions on kidney biopsy. Immunosuppressive therapies include steroids, mycophenolate, cyclophosphamide, Benlysta (belimumab), or Lupkynis (voclosporin).
Benlysta (belimumab) is a B-lymphocyte stimulator (BLyS)-specific inhibitor indicated for the treatment of:

- Those 5 years of age and older with active systemic lupus erythematosus (SLE) who are receiving standard therapy.
- Those 5 years of age and older with active lupus nephritis who are receiving standard therapy.

Benlysta is available as both an intravenous (IV) infusion and a subcutaneous (SC) injection.

- Preferred Formulation: The subcutaneous formulation of Benlysta (belimumab) is preferred over the intravenous formulation.
    - Vials are for intravenous administration only.
    - Autoinjectors and prefilled syringes are for subcutaneous administration only.
    - Vials are not intended for subcutaneous injection or autoinjectors/prefilled syringes for intravenous infusion.

  NOTE: For full dosage and administration information, please refer to the current prescribing information.
- Members should use the SC formulation unless specific exception criteria for IV administration are met (see Additional Exception Criteria for Intravenous Administration).
- Benlysta (belimumab) should be administered by a healthcare profession or trained caregiver for those 10 years of age or younger.

There is a risk of progressive multifocal leukoencephalopathy (PML), an opportunistic viral infection of the brain that can result in severe disability or death. Risk factors include presence of anti-JCV

antibodies, duration of therapy, and prior use of immunosuppressants. Concurrent use of immunosuppressants, antineoplastics and immunomodulatory therapies can increase the risk of PML and thus concomitant use is not recommended. If any new or deteriorating neurological signs and symptoms are identified, Benlysta (belimumab) should be stopped immediately and PML should be ruled out before continuing therapy.

Definitions

"Anti-JCV antibodies" are markers for exposure to the John Cunningham (JC) virus. If present, anti-JCV antibodies are associated with a higher risk of progressive multifocal leukoencephalopathy (PML), an opportunistic viral infection of the brain that can result in severe disability or death.

"Antimalarial" is a drug class that is used to treat malaria but also is used in autoimmune diseases such as lupus and rheumatoid arthritis.

"Autoantibody" is an antibody produced by one's own immune system that attacks the body's normal cells, rather than foreign antigens (such as viruses and bacteria).

"B cells" are cells in the body that help activate an immune response.

"B lymphocyte stimulator protein (BLyS)" is a molecule in the body that aids in the development of B cells.

"Central nervous system lupus" is a complication that can be seen in those with lupus and can involve conditions such as seizures, cerebrovascular accidents (strokes), delirium, and nerve pain.

"Corticosteroid" is a drug class that reduces inflammation and suppresses the immune system.

"Documentation" refers to written information, including but not limited to:

- Up-to-date chart notes, relevant test results, and/or relevant imaging reports to support diagnoses; or
- Prescription claims records, and/or prescription receipts to support prior trials of formulary alternatives.

"Human monoclonal antibody" is a protein made from human cells that is designed to bind to a specific molecule in the body and can be used to treat a variety of diseases including lupus, rheumatoid arthritis, and cancers.

"Immunosuppressives" are medications that prevent the actions of the immune system, used in diseases such as lupus, rheumatoid arthritis, psoriasis, and Crohn's disease.

"JCV" or "John Cunningham virus" refers to a virus associated with the development of progressive multifocal leukoencephalopathy (PML), a side effect of certain immunosuppressive medications. Those who use Benlysta should be tested for JCV before starting treatment and while on treatment to help identify if they are at a higher risk for PML.

"Lupus nephritis" is inflammation of the kidney in those with lupus.

"No evidence of" indicates that the reviewer has not identified any records of the specified item or condition within the submitted materials or claims history. In the absence of such evidence, the member is considered eligible. If any evidence of the item or condition is present upon review of the request, the member does not qualify.

"[s]" indicates state mandates may apply.

Clinical Indications

Medical Necessity Criteria for Clinical Review

General Medical Necessity Criteria

The Plan considers Benlysta (belimumab) medically necessary when ALL of the following criteria are met:

1. The member is 5 years of age or older; *AND*
2. No evidence the member has severe active central nervous system lupus (such as altered mental function or confusion, vision problems, or seizures); *AND*
3. Benlysta (belimumab) is being prescribed at a dose and frequency that is within FDA approved labeling OR is supported by compendia or evidence-based published dosing guidelines for the requested indication*; AND*

   The requested medication is being used within the Plan's Quantity Limit of: 4 pens every 28 days.
4. Recent (within the last 6 months) clinical chart documentation is provided for the below criteria when applicable*; AND*
5. The member meets the applicable Medical Necessity Criteria for Initial Clinical Review or Subsequent Clinical Review listed below.

Medical Necessity Criteria for Initial Clinical Review

Initial Indication-Specific Criteria

Active Systemic Lupus Erythematosus (SLE) who are Receiving Standard Therapy

The Plan considers Benlysta (belimumab) medically necessary when ALL of the following criteria are met:

6. The member meets the above General Medical Necessity Criteria; *AND*
7. The medication is being prescribed by a rheumatologist; *AND*
8. The member has a diagnosis of active systemic lupus erythematosus supported by the following:

a. Prior to initiating therapy, positive for autoantibodies relevant to SLE (e.g., antinuclear antibody [ANA] by IFA [Indirect Immunofluorescence Assay] 1:80 or higher, anti-double-stranded DNA [anti-dsDNA], anti-Smith, antiphospholipid antibodies [e.g., anti-RNP, anti-Ro, anti-La, or anti-cardiolipin], low complement proteins); *and*

9. The member is receiving standard therapy, which includes ONE (1) of the following, alone or in combination:
    a. antimalarials (e.g., hydroxychloroquine)*; or*
    b. corticosteroids (e.g., prednisone, methylprednisolone, dexamethasone); *or*
    c. immunosuppressives (e.g., azathioprine, methotrexate, mycophenolate, cyclosporine, cyclophosphamide)*; AND*
10. No evidence the member is using Benlysta (belimumab) in combination with ANY of the following:
    a. other biologic therapies (such as Actemra [toilizumab], Enbrel [etanercept], Humira [adalimumab], Stelara [ustekinumab]); *or*
    b. intravenous cyclophosphamide; *AND*
11. If the member is prescribed intravenous Benlysta (belimumab), meets the below Additional Exception Criteria for Intravenous Administration.

<u>Active Lupus Nephritis who are Receiving Standard Therapy.</u>

The Plan considers Benlysta (belimumab) medically necessary when ALL of the following criteria are met:

6. The member meets the above General Medical Necessity Criteria; *AND*
7. The medication is being prescribed by a rheumatologist or nephrologist; *AND*
8. The member has a diagnosis of active lupus nephritis supported by ONE of the following:
    a. Lupus nephritis confirmed on kidney biopsy*; or*
    b. Prior to initiating therapy, positive for autoantibodies relevant to SLE (e.g., antinuclear antibody [ANA] by IFA [Indirect Immunofluorescence Assay] 1:80 or higher, anti-double-stranded DNA [anti-dsDNA], anti-Smith, antiphospholipid antibodies [e.g., anti-RNP, anti-Ro, anti-La, or anti-cardiolipin], low complement proteins); *AND*
9. The member is receiving standard therapy, which includes ONE (1) of the following, alone or in combination:
    a. antimalarials (i.e., hydroxychloroquine)*; or*
    b. calcineurin inhibitors (e.g., cyclosporine, tacrolimus)*; or*
    c. corticosteroids (e.g., prednisone, methylprednisolone, dexamethasone); *or*
    d. immunosuppressives (e.g., azathioprine, cyclophosphamide, mycophenolate)*; AND*
10. No evidence the member is using Benlysta in combination with other biologic therapies (such as Actemra [toilizumab], Enbrel [etanercept], Humira [adalimumab], Stelara [ustekinumab]); *AND*
11. If the member is prescribed intravenous Benlysta (belimumab), meets the below Additional Exception Criteria for Intravenous Administration.

Additional Exception Criteria for Intravenous Administration

12. *The Plan requires all members to use Benlysta (belimumab) subcutaneous (SC) formulation for initial therapy and maintenance treatment.* Benlysta (belimumab) for intravenous (IV) infusion will be authorized only when the member meets ONE of the following:
    a. The member has a documented contraindication to the subcutaneous (SC) formulation that would NOT be expected to occur with the IV formulation; *OR*
    b. The member has demonstrated a clinical response to Benlysta SC but is unable to continue due to severe injection site reactions that are not manageable with standard interventions (e.g., persistent severe pain, recurrent large areas of erythema, severe pruritus unresponsive to treatment); *OR*
    c. The member experienced a documented intolerable adverse event to the SC formulation of Benlysta that would NOT be expected to occur with the IV formulation; *OR*
    d. The member has physical or cognitive limitations that prevent SC self-administration or administration by a caregiver, including but not limited to visual impairment, limited manual dexterity, or impaired cognitive function (documentation required); *OR*
    e. The member has a documented medical condition that significantly impairs subcutaneous absorption, making IV administration necessary for effective treatment (e.g., severe lipodystrophy, extensive scarring over injection sites, scleroderma with significant skin thickening); *OR*
    f. The member requires a dose that is NOT available or feasible for SC administration; *OR*
    g. The prescriber provides a clear clinical rationale, supported by documentation, for why Benlysta IV is expected to be beneficial despite failure or intolerance of Benlysta SC.

If the above prior authorization criteria are met, the requested product will be approved for up to 12-months.[5]

➢ *Subcutaneous administration is the preferred route and should be used for initial therapy and maintenance treatment unless exception criteria for IV administration are met.*

Continued Care

Medical Necessity Criteria for Subsequent Clinical Review

Subsequent Indication-Specific Criteria

Active Systemic Lupus Erythematosus (SLE) who are Receiving Standard Therapy OR Active Lupus Nephritis who are Receiving Standard Therapy.

The Plan considers Benlysta (belimumab) medically necessary when ALL of the following criteria are met:

1. The member meets the above applicable General Medical Necessity Criteria and/or Initial Clinical Review; *AND*
2. Recent chart documentation (within the last 6 months) demonstrates ONE of the following:

a. The member has shown a clinical improvement (e.g., sustained improvement in disease activity and reductions in disease flares) in symptoms since starting the requested medication*; or*
b. The member has experienced disease stability (e.g., complete remission, low disease activity state, no new lupus disease activity compared with the previous assessment) since starting the requested medication.

If the above reauthorization criteria are met, the requested product will be approved for up to 12-months.[s]

Experimental / Investigational or unproven[s]

Benlysta (belimumab) for any other indication is considered experimental, investigational, or unproven. Non-covered indications include, but are not limited to, the following:

- Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis / Granulomatosis With Polyangiitis. One multicentre double-blind randomized controlled study did not find a signficant benefit in reducing vasculitis relapse in those treated with Benlysta (belimumab) plus azathioprine and glucocorticoids compared to placebo. There are no high quality, large controlled trials with published results to support the safety and efficacy of Benlysta (belimumab) for the management of Granulomatosis With Polyangiitis.
- Anti-Phospholipids Syndrome (APS). There is currently no high quality published data to support the safety and efficacy of Benlysta (belimumab) for the management of APS.
- Chronic Obstructive Pulmonary Disease (COPD) / Emphysema. There are no high quality, large controlled trials with published results to support the safety and efficacy of Benlysta (belimumab) for the management of COPD/emphysema. One small (n=17) "proof-of-concept" study (NCT03244059) did not assess clinical outcomes, only surrogate markers of disease (circulating B-cells, pneumococcal polysaccharide-binding antibodies, and circulating anti-GRP78 immuneglobulin-G levels).
- Cryoglobulinemia. Small studies and case reports find some promising results with Benlysta (belimumab), however there are currently no high quality published data to support the safety and efficacy of Benlysta (belimumab) for the management of cryoglobulinemia.
- Discoid Lupus Erythematosus (DLE). There is currently no high quality published data to support the safety and efficacy of Benlysta (belimumab) for the management of DLE.
- Graft-versus-host Disease (GVHD). There is currently no high quality published data to support the safety and efficacy of Benlysta (belimumab) for the prevention or management of GVHD.
- Idiopathic CD4 Lymphocytopenia. There is currently no high quality published data to support the safety and efficacy of Benlysta (belimumab) for the management of idiopathic CD4 lymphocytopenia.
- Idiopathic inflammatory myopathy. There is a small, 17 patient placebo controlled trial showing a trend toward moderate improvement in myositis patients vs. placebo. There are no high quality,

large controlled trials with published results to support the safety and efficacy of Benlysta (belimumab) for idiopathic inflammatory myopathy.

- Immune Thrombocytopenia (ITP). Benlysta (belimumab) has been studied in small cohort studies, case reports, and case series in those with ITP and SLE. While there have been promising results in these published studies, there are no high quality, large controlled trials with published results to support the safety and efficacy of Benlysta (belimumab) for the management of ITP, outside of the management of SLE.
- Immunoglobulin G4 Related Sclerosing Disease. There have only been case reports of the use of Benlysta (belimumab) for the management of Immunoglobulin G4 Related Sclerosing Disease in those who already have SLE. There are currently no high quality published data to support the safety and efficacy of Benlysta (belimumab) for the management of Immunoglobulin G4 Related Sclerosing Disease, outside of the management of SLE
- Myasthenia Gravis. One small (n=40), phase II randomized controlled trial assessed Benlysta (belimumab) versus placebo and did not find a significant improvement in the primary outcome of change from baseline in the quantitative myasthenia gravis scale at week 24. There are no high quality, large controlled trials with published results to support the safety and efficacy of Benlysta (belimumab) for the management of myasthenia gravis.
- Neuromyelitis Optica Spectrum Disorders. There is currently no high quality published data to support the safety and efficacy of Benlysta (belimumab) for the prevention or management of neuromyelitis optica spectrum disorders.
- Relapsed Chronic Lymphocytic Leukemia (CLL). There is currently no high quality published data to support the safety and efficacy of Benlysta (belimumab) for the management of relapsed CLL.
- Rheumatoid Arthritis. In one phase II randomized controlled trial (n=238), Benlysta (belimumab) showed inconsistent benefit amongst those with moderate rheumatoid arthritis who had failed at least one (1) disease-modifying antirheumatic drug (DMARD) compared to placebo. An extension study was terminated, and did not publish results assessing long-term benefits (NCT00583557).
- Sjogren's Syndrome (SS). In a small (n=86) double-blind randomized multicentre clinical study (NCT02631538) there were inconsistent and non-significant improvements in Sjogren's Syndrome disease activity scores in both the Benlysta (belimumab) and Benlysta (belimumab) and Rituximab (Rituxan) combined arms versus placebo. All other studies showing positive and/or promising responses were of low quality and included a very small number of participants. There are no high quality, large controlled trials with published results to support the safety and efficacy of Benlysta (belimumab) for the management of Sjogren's Syndrome (SS).
- Vasculitis. Vasculitis can be a manifestation of SLE, and small studies have shown some benefit in vasculitis resolution in those with SLE. However, a multicentre double-blind randomized controlled study did not find a significant benefit in reducing vasculitis relapse in those treated with Benlysta (belimumab) plus azathioprine and glucocorticoids compared to placebo. There are currently no other high quality published data to support the safety and efficacy of Benlysta (belimumab) for the management of vasculitis, outside of the management of SLE.

Not Medically Necessary[s]

The Plan requires all members to use the subcutaneous formulation of Benlysta for initial therapy and maintenance treatment, unless specific exception criteria for intravenous administration are met and documented (see Additional Exception Criteria for Intravenous Administration). Use of the intravenous formulation without meeting these criteria or continuing intravenous administration when transition to subcutaneous administration is feasible is considered not medically necessary.

Applicable Billing Codes

Table 1	
CPT/HCPCS codes considered medically necessary if criteria are met:	
Code	*Description*
J0490	Benlysta IV Injection, belimumab, 10 mg
J3590	Benlysta SC (belimumab) Unclassified biologics

Table 2	
ICD-10 diagnosis codes considered medically necessary with Table 1 (CPT/HCPCS) codes if criteria are met:	
Codes	*Description*
Systemic Lupus Erythematosus	
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
M32.15	Tubulo-interstitial nephropathy in systemic lupus erythematosus
M32.19	Other organ or system involvement in systemic lupus erythematosus

Table 2	
ICD-10 diagnosis codes considered medically necessary with Table 1 (CPT/HCPCS) codes if criteria are met:	
Codes	*Description*
M32.8	Other forms of systemic lupus erythematosus
M32.9	Systemic lupus erythematosus, unspecified
Lupus Nephritis	
M32.14	Glomerular disease in systemic lupus erythematosus

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Clinical Guideline Revision / History Information

Original Date: 08/06/2020

Reviewed/Revised: 06/24/2021, 12/01/2021, 06/23/2022, 9/15/2022, 9/21/2023, 8/29/2024, 12/01/2025, 08/03/2026