Belimumab

Coverage Policy

Belimumab (Benlysta®) is considered medically necessary when all of the following criteria are met:

- Individual is 5 years of age or older
- Diagnosis of active systemic lupus erythematosus (SLE)
- Positive autoantibody test (i.e., anti-nuclear antibody [ANA] greater than or equal to 1:80 and/or anti-double-stranded DNA [anti-dsDNA] greater than or equal to 30 IU/ml)
- Failure/inadequate response to standard therapy for SLE with any of the following:
  - Hydroxychloroquine
  - Immunosuppressant agents (for example, oral cyclophosphamide, azathioprine, mycophenolate, methotrexate, cyclosporine)
  - Corticosteroids (for example, methylprednisolone, prednisone)
- Used concurrently with at least one of the following: (unless the patient is determined to be intolerant due to a significant toxicity, as determined by the prescribing physician):
  - Hydroxychloroquine
  - Immunosuppressant agents (for example, oral cyclophosphamide, azathioprine, mycophenolate, methotrexate, cyclosporine)
  - Corticosteroids (for example, methylprednisolone, prednisone)
• Prescribed by or in consultation with rheumatologist, clinical immunologist, nephrologist, neurologist, or dermatologist

Initial and reauthorization is up to 12 months unless otherwise stated.

Belimumab (Benlysta®) is considered medically necessary for continued use when the following are met:
• Initial criteria for use has been met
• Individual has responded to Benlysta subcutaneous or intravenous (for example, reduction in flares, reduction in corticosteroid dose, decrease of anti-dsDNA titer, improvement in specific organ dysfunction [for example, musculoskeletal, blood, hematologic, vascular, others])

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.

Belimumab (Benlysta®) is considered experimental, investigational or unproven for ANY other use including the following:
• Anti-neutrophil cytoplasmic antibodies (ANCA) positive vasculitis (i.e., Wegener’s granulomatosis and microscopic polyangiitis)
• Concomittant use with Biological DMARD (for example, tumor necrosis factor inhibitors)
• Primary Sjogren’s syndrome
• Rheumatoid arthritis
• Severe active lupus nephritis
• Severe active central nervous system lupus
• Waldenstrom macroglobulinemia

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

**FDA Approved Indications**

**FDA Approved Indication**
Benlysta (belimumab) 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.

Limitations 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.

**Recommended Dosing**

**FDA Recommended Dosing**
Benlysta may be administered as an intravenous infusion in patients aged 5 years and older or as a subcutaneous injection in patients aged 18 years and older. Vials are intended for intravenous use only (not for subcutaneous use) and autoinjectors and prefilled syringes are intended for subcutaneous use only (not for intravenous use).

<table>
<thead>
<tr>
<th>Formulation</th>
<th>FDA Recommended Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravenous</td>
<td>Recommended Intravenous Dosage Regimen — Adult and Pediatric Patients Benlysta for intravenous use must be reconstituted and diluted prior to administration. Do not administer as an intravenous push or bolus. The recommended intravenous dosage regimen is 10 mg/kg at 2-week intervals for the first 3 doses and at 4-week intervals thereafter. Reconstitute, dilute, and administer as an intravenous infusion over a period of 1 hour. The infusion rate may be slowed or</td>
</tr>
</tbody>
</table>
interrupted if the patient develops an infusion reaction. The infusion must be discontinued immediately if the patient experiences a serious hypersensitivity reaction.

**Subcutaneous**

Subcutaneous dosing of BENLYSTA has not been evaluated and is not approved for patients younger than 18 years of age.

Recommended Subcutaneous Dosage Regimen — Adult Patients

The recommended dosage is 200 mg once weekly given as a subcutaneous injection in the abdomen or thigh. Subcutaneous dosing is not based on weight. If transitioning from intravenous therapy with BENLYSTA to subcutaneous administration, administer the first subcutaneous dose 1 to 4 weeks after the last intravenous dose.

**Drug Availability**

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Drug Availability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravenous</td>
<td>For injection: 120 mg or 400 mg lyophilized powder in single-dose vials for reconstitution and dilution prior to intravenous infusion</td>
</tr>
<tr>
<td>Subcutaneous</td>
<td>Injection: 200 mg/mL as a clear to opalescent, and colorless to pale yellow solution in a single-dose prefilled autoinjector or a single-dose prefilled glass syringe.</td>
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</tbody>
</table>

**General Background**

**Pharmacology**

Belimumab is a human IgG 1-lambda monoclonal antibody that binds to the B-lymphocyte stimulator (BLyS) protein to inhibit it from binding to B cells. B-lymphocyte stimulator protein plays a role in the survival of B-cells. Without the BLyS protein, fewer B-cells differentiate into plasma cells that produce autoantibodies. (McEvoy, 2017)

**Professional Societies/Organizations**

**American College of Rheumatology (ACR)**

The ACR criteria for classification of SLE are used to identify patients for clinical studies and requires 4 of 11 criteria at some point in their medical history for an individual to be considered as having SLE. Additionally, these criteria are often used in clinical practice as a guide to help facilitate the diagnosis of SLE. The criteria are contained in the following table:

<table>
<thead>
<tr>
<th>Item</th>
<th>Definition/Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malar Rash</td>
<td>Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds</td>
</tr>
<tr>
<td>Discoid rash</td>
<td>Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions</td>
</tr>
<tr>
<td>Photosensitivity</td>
<td>Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation</td>
</tr>
<tr>
<td>Oral ulcers</td>
<td>Oral or nasopharyngeal ulceration, usually painless, observed by a physician</td>
</tr>
<tr>
<td>Nonerosive arthritis</td>
<td>Involving 2 or more peripheral joints, characterized by tenderness, swelling or effusion</td>
</tr>
<tr>
<td>Pleuritis or Pericarditis</td>
<td>Pleuritis – convincing history of pleuritic pain or rub heard by a physician or evidence of pleural effusion</td>
</tr>
<tr>
<td></td>
<td>Pericarditis – documented by electrocardiogram or rub or evidence or pericardial effusion</td>
</tr>
<tr>
<td>Item</td>
<td>Definition/Description</td>
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</tbody>
</table>
| Renal disorder          | One of the following:  
  • Persistent proteinuria > 0.5gm/d or >3+ if quantitation not performed  
  • Cellular casts – may be red cell, hemoglobin, granular, tubular, or mixed                                                                                                                                 |
| Neurologic disorder     | One of the following:  
  • Seizures – in the absence of offending drugs or known metabolic derangement, e.g., uremia, ketoacidosis, or electrolyte imbalance  
  • Psychosis – in the absence of offending drugs or known metabolic derangement, e.g., uremia, ketoacidosis, or electrolyte imbalance                                                                 |
| Hematologic Disorder    | One of the following:  
  • Hemolytic anemia with reticulocytosis  
  • Leukopenia - < 4,000/mm³ on ≥ 2 occasions  
  • Lymphopenia - < 1,500/mm³ on ≥ 2 occasions  
  • Thrombocytopenia - < 100,000/mm³ in the absence of offending drug                                                                                                                                 |
| Immunologic Disorder    | One of the following:  
  • Anti-DNA: antibody to native DNA in abnormal titer  
  • Anti-Sm: presence of antibody to Sm nuclear antigen  
  • Positive finding of antiphospholipid antibodies based on:  
    o Abnormal serum level of IgG or IgM anticardiolipin antibodies  
    o A positive test result for lupus anticoagulant using a standard method  
    o A false-positive test result for at least 6 months and confirmed by Treponema pallidum immobilization or fluorescent treponemal antibody absorption tests                                                                 |
| Positive antinuclear antibody | An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time in the absence of drug                                                                                     |

Guidelines for lupus nephritis from the American College of Rheumatology (ACR) [2012] do not address Benlysta’s place in therapy. (Hahn, 2012)

**European League Against Rheumatism (EULAR)**
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). EULAR defines an inadequate response as residual disease activity not allowing tapering of glucocorticoids and/or frequent relapses. (Fanouriakis, 2019)

**The American Board of Internal Medicine’s (ABIM) Foundation Choosing Wisely® Initiative**
No recommendations are available for Belimumab (Benlysta).

**Centers for Medicare & Medicaid Services - National Coverage Determinations (NCDs)**
There are no CMS National Coverage Determinations for Belimumab (Benlysta).

**Clinical Efficacy**
To date there are no clinical trials comparing belimumab with other agents used to treat SLE. A phase II dose finding study compared standard treatment plus belimumab 1 mg/kg, 4 mg/kg, 10 mg/kg, and placebo in 449 patients. Primary outcomes evaluated the percent change in SELENA-SLEDAI score at week 24 and time to first flare at week 52. No dose of belimumab was significantly different compared to placebo in either primary efficacy endpoint. However, a subgroup analysis of percent change in SELENA-SLEDAI at week 52 showed the
combined belimumab groups to be significantly different compared to placebo in 321 patients who were serologically active. (Wallace, 2009) This significant difference led to the development of two phase III trials.

The two phase III, multicenter, randomized, double blind, placebo-controlled trials which were conducted are Belimumab International SLE Study (BLISS)-52 and BLISS-76. BLISS-52 evaluated 865 patients. BLISS-76 evaluated 819 patients. Both trials compared standard treatment plus either belimumab 1 mg/kg, 10 mg/kg, or placebo. The primary outcome in both trials was the SRI response rate at week 52. The SRI response rate for belimumab 10 mg/kg was significantly improved compared to placebo at week 52 in both trials. A secondary endpoint for BLISS-76 was the SRI response rate at week 76 which was not significantly different compared to placebo. This result may be due to an increased rate of dropouts in the belimumab group compared to the placebo group between week 52 and week 76. Response rates for belimumab 1 mg/kg were not consistent in both BLISS trials. Belimumab 1 mg/kg was significantly improved compared to placebo for SRI response rate at week 52 in BLISS-52; however, there was no difference in SRI response rate between belimumab 1 mg/kg and placebo at week 52 in BLISS-76. (CDER 2011; Navarra, 2011)

Experimental, Investigational, Unproven Uses
Belimumab has been evaluated in a phase II clinical trial for individuals with rheumatoid arthritis who have failed at least one disease-modifying antirheumatic drug (DMARD). Compared to placebo significantly more belimumab-treated patients (dose groups 1 mg/kg and 10 mg/kg) had a 20% improvement in American College of Rheumatology criteria (ACR20). (Stohl, 2013) Belimumab was also evaluated and found to be effective in a small (n = 30), phase II, open-label trial in primary Sjogren’s syndrome. (Mariette, 2015) A phase II, single-arm trial in 12 patients with Waldenstrom macroglobulinemia did not produce any disease responses with belimumab (10 of the patients had stable disease for a median duration of 6.75 months). (Bishton, 2013)

Phase III studies to evaluate belimumab in ANCA positive vasculitis (Wegener’s granulomatosis and microscopic polyangiitis) and in active lupus nephritis are ongoing. (Human Genome Sciences Inc.)

Coding/ Billing Information

Note: 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

<table>
<thead>
<tr>
<th>HCPCS Codes</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>J0490</td>
<td>Injection, belimumab, 10 mg</td>
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References