Clinical Policy Bulletin: Belimumab (Benlysta)

Number: 0818

Policy

Note: REQUIRES PRECERTIFICATION*

Aetna considers belimumab (Benlysta) medically necessary for the treatment of adults (aged 18 years or older) with active systemic lupus erythematosus and positive autoantibody test (e.g., 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) and who are receiving standard therapy comprising any of the following (alone or in combination): antimalarials, corticosteroids, immunosuppressives (excluding intravenous cyclophosphamide), and non-steroidal anti-inflammatory drugs, and with no exclusion criteria.

Aetna considers belimumab experimental and investigational for all other indications including the following (not an all-inclusive list) because its effectiveness for indications other than the one listed above has not been established:

- Antibody-associated vasculitis
- Anti-phospholipid antibody syndrome
- Immunosuppression following stem cell/solid organ transplantations
- Multiple sclerosis
- Myasthenia gravis
- Rheumatoid arthritis
- Sjogren syndrome
- Uveitis
- Waldenstrom macroglobulinemia

Exclusion Criteria for Belimumab:

Individuals with active severe central nervous system (CNS) lupus (including seizures, psychosis, organic brain syndrome, cerebrovascular accident, cerebritis or CNS vasculitis requiring therapeutic intervention within 60 days before initiation of belimumab); or
Belimumab (Benlysta)

- Individuals with active severe lupus nephritis (proteinuria greater than 6 g/24 hour, or serum creatinine greater than 2.5 mg/dL); or
- Individuals who require hemodialysis; or
- Individuals who require high-dose prednisone greater than 100 mg/day; or
- Use in combination with other biologics or intravenous cyclophosphamide

Please see appendix for selection criteria.

**Note:** Precertification of belimumab is required of all Aetna participating providers and members in applicable plan designs. For precertification of belimumab, call (866) 503-0857, or fax (866) 267-3277

**Note:** Pharmacy has a maximum coverage of belimumab for 1 year. Additional therapy will be authorized at 6 month intervals if there is documentation of continued improvement in disease activity indicating a therapeutic response/stability of the disease.

**Background**

Systemic lupus erythematosus (SLE) is a potentially fatal, autoimmune disease, which is characterized by clinical diversity, alterations in the disease activity over time, and aberrations in multiple components of the immune system including B cells, T cells, as well as cytokines and growth factors, especially the presence of anti-nuclear antibodies (ANA) that are found in over 90% of the patients. Moreover, anti-double-strand deoxyribonucleic acid (anti-dsDNA) antibodies are found in 50 to 90% of the patients. The prevalence of SLE worldwide is 4 to 250 per 100,000; the disease affects women disproportionately (approximately 90% of the patients are female). The incidence is most frequent in women aged 15 to 25 years. The disease affects many parts of the body including the brain, heart, joints, kidneys, lungs, and the skin. When SLE flares, it can present as chest pain, fatigue, fever, hair loss, rash, light sensitivity, as well as swelling in the joints and joint pain (Finnish Medical Society, 2007).

Conventional treatments of SLE include anti-malarials (e.g., chloroquine and hydroxychloroquine), corticosteroids, and non-steroidal anti-inflammatory drugs (e.g., aspirin). While therapeutic advances in immunosuppressive drugs (e.g., azathioprine, cyclophosphamide, methotrexate, mycophenolate) and support therapy have markedly improved survival, SLE still carries substantially increased rates of mortality and end stage renal disease, which are even more elevated in younger patients. No new drugs have been approved for SLE in over 50 years. Hence, a lot of hope and excitement has been generated by the development of biological agents designed to eliminate B cells either through direct killing (anti-B cell antibodies such as rituximab) or attrition by inhibition of survival (anti-B-lymphocyte stimulator BLyS [also known as BAFF] agents such as belimumab). Belimumab is a human IgG1g antibody that is the first of the BLyS-specific inhibitor. It blocks the binding of soluble BLyS, a B-cell survival factor, to its receptors on B cells. Belimumab does not bind B cells directly, but by binding BLyS, belimumab inhibits the survival of B cells, including auto-reactive B cells, and reduces the differentiation of B cells into immunoglobulin-producing plasma cells. Clinical trials of various phases have indicated that belimumab is beneficial for patients with SLE (Furie et al, 2008; Wallace et al, 2009; Jacobi et al, 2010; Navarra et al, 2011).
In a phase I clinical study, Furie et al (2008) evaluated the safety, biological activity, and pharmacokinetics of belimumab in patients with SLE. A total of 70 patients with mild-to-moderate SLE were randomized to receive placebo (n = 13) or belimumab (n = 57) at 4 different doses (1.0, 4.0, 10, and 20 mg/kg body weight) as a single infusion or two infusions 21 days apart. Patients were followed for 84 to 105 days to assess adverse events, pharmacokinetics, peripheral blood B-cell counts, serology, and SLE disease activity. Data from the study were summarized using descriptive statistics. Chi-square type tests were used to analyze discrete variables. The Kruskal-Wallis test, the Wilcoxon test, and the analysis of co-variance were used to analyze the continuous variables, as appropriate. The analysis was performed on all randomized patients who received study agent. The incidences of adverse events and laboratory abnormalities were similar among the belimumab and placebo groups. Belimumab pharmacokinetics were linear across the 1.0 to 20 mg/kg dose range. Long terminal elimination half-life (8.5 to 14.1 days), slow clearance (7 ml/day per kg), and small volume of distribution (69 to 112 ml/kg) were consistent with a fully human antibody. Significant reductions in median percentages of CD20+ B cells were observed in patients treated with a single dose of belimumab versus placebo (day 42: p = 0.0042; and day 84: p = 0.0036) and in patients treated with 2 doses of belimumab versus placebo (day 105: p = 0.0305); SLE disease activity did not change after 1 or 2 doses of belimumab. The authors concluded that belimumab was well-tolerated and reduced peripheral B-cell levels in SLE patients.

In a phase II, randomized, double-blind, placebo-controlled, dose-ranging study, Wallace and colleagues (2009) evaluated the safety, tolerability, biological activity, and effectiveness of belimumab in combination with standard of care therapy (SOC) in patients with active SLE. Patients with a Safety of Estrogens in Lupus Erythematosus: National Assessment (SELENA) version of the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score greater than or equal to 4 (n = 449) were randomly assigned to belimumab (1, 4, or 10 mg/kg) or placebo in a 52-week study. Co-primary end points were the percent change in the SELENA-SLEDAI score at week 24 and the time to first SLE flare. Significant differences between the treatment and placebo groups were not attained for either primary end point, and no dose response was observed. Reductions in SELENA-SLEDAI scores from baseline were 19.5 % in the combined belimumab group versus 17.2 % in the placebo group. The median time to first SLE flare was 67 days in the combined belimumab group versus 83 days in the placebo group. However, the median time to first SLE flare during weeks 24 to 52 was significantly longer with belimumab treatment (154 versus 108 days; p = 0.0361). In the subgroup (71.5 %) of serologically active patients (ANA titer greater than or equal to 1:80 and/or anti-dsDNA greater than or equal to 30 International Units/ml), belimumab treatment resulted in significantly better responses at week 52 than placebo for SELENA-SLEDAI score (-28.8 % versus -14.2 %; p = 0.0435), physician's global assessment (-32.7 % versus -10.7 %; p = 0.0011), and Short Form-36 physical component score (+3.0 versus +1.2 points; p = 0.0410). Treatment with belimumab resulted in a 63 to 71 % reduction of naive, activated, and plasmacytoid CD20+ B cells, and a 29.4 % reduction in anti-dsDNA titers (p = 0.0017) by week 52. The rates of adverse events and serious adverse events were similar in the belimumab and placebo groups. The authors concluded that belimumab was biologically active and well-tolerated. The effect of belimumab on the reduction of SLE disease activity or flares was not significant. However, serologically active SLE patients responded significantly better to belimumab therapy plus SOC than to SOC alone.
Jacobi and co-workers (2010) examined the effects of long-term BLyS inhibition in patients with SLE. A total of 17 subjects with SLE who were enrolled in a clinical trial of belimumab plus SOC were studied. Phenotypic analysis of lymphocytes was performed using flow cytometry. Circulating antibody-secreting cells were enumerated using enzyme-linked immunosorbent assay. Serum was analyzed by enzyme-linked immunosorbent assay using an antibody that recognizes products of the V(H)4-34 gene. Lymphocyte counts, Ig levels, and anti-dsDNA antibody levels were available as part of the clinical trial analyses. Samples were collected on days 0, 84, 168, 365, and 532 and after day 730. The total number of B cells started to decrease from baseline between days 84 and 168. This was due to a decrease in naive and transitional B cells. CD27+IgD+ memory B cells and plasmablasts decreased only after 532 days, whereas CD27+IgD- memory B cells were not affected, and there were no changes in T cells. Serum IgM levels began to decline between days 84 and 168, but there were no changes in serum levels of IgG, IgG anti-dsDNA antibodies, or V(H)4-34 antibodies during the study. Patients with SLE had more IgM-, IgG-, and autoantibody-producing B cells than did normal controls on day 0. There was only a modest decrease in the frequency of total IgM-producing, but not IgG-producing, cells on days 365 and 532, consistent with the phenotypic and serologic data. The authors concluded that these findings confirm the dependence of newly formed B cells on BLyS for survival in humans. In contrast, memory B cells and plasma cells are less susceptible to selective BLyS inhibition.

In a randomized, multi-center, placebo-controlled, phase III trial, Navarra and associates (2011) evaluated the safety and effectiveness of belimumab in patients with active SLE. Patients (aged greater than or equal to 18 years) who were sero-positive with scores of at least 6 on the SELENA-SLEDAI were enrolled in the study. Patients were randomly assigned by use of a central interactive voice response system in a 1:1:1 ratio to belimumab 1 mg/kg or 10 mg/kg, or placebo by intravenous infusion in 1 hr on days 0, 14, and 28, and then every 28 days until 48 weeks, with SOC. Patients, investigators, study coordinators, and sponsors were masked to treatment assignment. Primary efficacy end point was improvement in the SLE Responder Index (SRI) at week 52 (reduction greater than or equal to 4 points in SELENA-SLEDAI score; no new British Isles Lupus Assessment Group [BILAG] A organ domain score and no more than 1 new B organ domain score; and no worsening [less than 0·3 increase] in Physician's Global Assessment [PGA] score) versus baseline. Method of analysis was by modified intention-to-treat. A total of 867 patients were randomly assigned to belimumab 1 mg/kg (n = 289) or 10 mg/kg (n = 290), or placebo (n = 288); 865 were treated and analyzed in the belimumab (1 mg/kg, n = 288; 10 mg/kg, n = 290) and placebo groups (n = 287). Significantly higher SRI rates were noted with belimumab 1 mg/kg (148 [51 %], odds ratio 1.55 [95 % confidence interval [CI]: 1.10 to 2.19]; p = 0·0129) and 10 mg/kg (167 [58 %], 1.83 [1.30 to 2.59]; p = 0·0006) than with placebo (125 [44 %]) at week 52. More patients had their SELENA-SLEDAI score reduced by at least 4 points during 52 weeks with belimumab 1 mg/kg (153 [53 %], 1.51 [1.07 to 2.14]; p = 0·0189) and 10 mg/kg (169 [58 %], 1.71 [1.21 to 2.41]; p = 0·0024) than with placebo (132 [46 %]). More patients given belimumab 1 mg/kg (226 [78 %], 1.38 [0.93 to 2.04]; p = 0·1064) and 10 mg/kg (236 [81 %], 1.62 [1.09 to 2.42]; p = 0·0181) had no new BILAG A or no more than 1 new B flare than did those in the placebo group (210 [73 %]). No worsening in PGA score was noted in more patients with belimumab 1 mg/kg (227 [79 %], 1.68 [1.15 to 2.47]; p = 0·0078) and 10 mg/kg (231 [80 %], 1.74 [1.18 to 2.55]; p = 0·0048) than with placebo (199 [69 %]). Rates of adverse events were similar in the groups given belimumab 1 mg/kg and 10 mg/kg, and placebo: serious infection was reported in 22 (8 %), 13 (4 %), and 17 (6 %).
patients, respectively, and severe or serious hypersensitivity reactions on an infusion day were reported in 2 (less than 1 %), 2 (less than 1 %), and no patients, respectively. No malignant diseases were reported. The authors concluded that belimumab has the potential to be the first targeted biological treatment that is approved specifically for SLE, providing a new option for the management of this important prototypic autoimmune disease.

On March 8, 2011, the U.S. Food and Drug Administration approved belimumab (Benlysta) for the treatment of adult patients with active, autoantibody-positive systemic lupus erythematosus who are receiving standard therapy, including anti-malarials, corticosteroids, immunosuppressives, and non-steroidal anti-inflammatory drugs. The label for Benlysta includes the following limitations of use: The efficacy of belimumab has not been evaluated in patients with severe active lupus nephritis or severe active central nervous system lupus, and has not been studied in combination with other biologics or intravenous cyclophosphamide. Belimumab is administered intravenously over a 1-hour period; it should not be administered with live vaccines. The most common side effects associated with the use of belimumab include diarrhea, fever, and nausea. Patients also commonly experienced infusion reactions; thus, pre-treatment with an anti-histamine should be considered. Belimumab is approved at a dosage of 10 mg/kg of body weight to be given at 2-week intervals for the first 3 doses and 4-week intervals thereafter. In several randomized controlled trials examining the effectiveness of belimumab in patients with SLE, the durations of therapy were 52 and 76 weeks (Phung, 2011). In a clinical study of belimumab submitted to the FDA for approval, active SLE disease was defined as a SELENA-SLEDAI (Safety of Estrogens in Lupus Erythematosus: National Assessment-Systemic Lupus Erythematosus Disease Activity Index) score of equal to or greater than 4, and positive autoantibody test results (anti-nuclear antibody [ANA] and/or anti-double-stranded DNA [anti-dsDNA]) at screening.

Belimumab has also been studied in the treatment of other autoimmune diseases such as lupus nephritis, multiple sclerosis, and rheumatoid arthritis (Aran and Putterman, 2008; Hawker, 2008; Bingham, 2008). Furthermore, belimumab is being considered as one of the novel strategies in immunosuppression following stem cell/solid organ transplantations (Webber et al, 2011). However, in the absence of evidence based on large, randomized, placebo-controlled trials, the role of belimumab for these indications has yet to be established.

The American College of Rheumatology's guidelines for screening, treatment, and management of lupus nephritis (Hahn et al, 2012) notes that alternative therapies (e.g., rituximab, tacrolimus, belimumab, calcineurin inhibitors) were considered but no consensus for recommendation was reached.

Khattri and colleagues (2012) stated that the increased awareness of the role of humoral immunophysiology in anti-phospholipid syndrome (APS) has aroused interest in B cells as therapeutic targets in this disease. These researchers reviewed the literature on B cell-directed therapies in human and experimental APS. The clinical data were limited to B cell depletion with rituximab and comprised case reports and case series. Murine studies include use of modulators of B cell function (e.g., belimumab and abatacept). In both human and murine studies, B cell-directed therapies appeared to have clinical and serologic beneficial effects including a decrease in the anti-phospholipid antibody titers after treatment. The authors concluded that randomized controlled trials are needed to
examine if B cell depletors and/or B cell modulators can be effective agents for treating patients with APS.

Diaz-Manera et al (2012) stated that new treatments for immune mediated diseases have increased notably in the last 10 years. Monoclonal antibodies directed against different components of the immune system have appeared, along with new drugs from the hematology field. In the case of myasthenia gravis (MG), many of these new treatments have been used in experimental animal models and also in patients. These investigators reviewed the progress in the field of MG treatment achieved in the last 5 years. Firstly, the current treatment protocol was introduced. Secondly, new data from recent randomized trials and case series of patients treated with methotrexate, cyclophosphamide, rituximab or improved systems of apheresis was reported. Finally, all future treatments that are currently under evaluation in pre-clinical animal models of experimental autoimmune MG were discussed. Evidence supporting the use of methotrexate and rituximab in MG has been published recently, in addition to conflicting randomized trials that were not successful, evaluating the use of tacrolimus as a steroid sparing agent. New promising therapies (e.g., belimumab and eculizumab) are currently under evaluation in clinical trials.

O’Neill and Scully (2013) noted that biologic therapy has a potential to benefit patients with orofacial manifestations of Sjogren syndrome (SS). The most appropriate use of biologics would appear to be in patients with severe or multi-system features of SS, but their use early in the pathogenesis has the potential to prevent disease progression. Tumor necrosis factor-alpha blockade has not proven effective in SS. B-cell depletion using rituximab has been of benefit, mainly in relation to extra-glandular features, and to some extent in relation to hypo-salivation where there is still residual salivary function. Rituximab is also effective in the treatment of SS-associated (extra-salivary) lymphomas, although the therapeutic response in salivary lymphoma is poorer. Rituximab is given as a single or periodic intravenous infusion. Potential adverse effects exist, notably infusion reactions and infection, and so a full risk/benefit analysis is indicated for prospective patients. The authors concluded that further studies of rituximab in SS are ongoing, and newer agents under trial include belimumab.

Jin and Ding (2013) summarized up-to-date pharmacological and clinical data of belimumab in the treatment of rheumatoid arthritis (RA). A literature search was performed on PubMed using keywords, including belimumab, LymphoStat-B, benlysta, BLyS inhibitor, rheumatoid arthritis and autoimmune disease. References of relevant studies were searched by hand. Abstracts of international conferences up to October 2012 were also included. Belimumab was well-tolerated in the treatment of RA over 24 weeks. It significantly increased American College of Rheumatology (ACR)20 responses at week 24, especially in patients with high disease activity, positive rheumatoid factor, no anti-TNF treatment experience and those who had failed methotrexate therapy. However, belimumab failed to demonstrate significantly improved ACR50 and ACR70 responses in the single phase II clinical trial of RA. The authors concluded that these results suggested that the clinical effectiveness of belimumab for RA needs to be further investigated in future clinical trials. Careful patient selection may be necessary for belimumab to achieve optimal clinical outcomes in RA.

Mariette et al (2013) evaluated the safety and effectiveness of belimumab in patients with primary Sjogren's syndrome (pSS). Patients were included in this bi-centric prospective 1-year open-label trial if they fulfilled American European Consensus group criteria, were
anti-Sjogren’s syndrome A-positive and had current systemic complications or salivary gland enlargement, or early disease (less than 5 years), or biomarkers of B cell activation. They received belimumab, 10 mg/kg, at weeks 0, 2 and 4 and then every 4 weeks to week 24. The primary end-point, assessed at week 28, was improvement in 2 of 5 items: reduction in greater than or equal to 30 % in dryness score on a visual analog scale (VAS), greater than or equal to 30 % in fatigue VAS score, greater than or equal to 30 % in VAS pain score, greater than or equal to 30 % in systemic activity VAS assessed by the physician and/or greater than 25 % improvement in any B cell activation biomarker values. Among 30 patients included, the primary end-point was achieved in 18 (60 %). The mean (SD) European League Against Rheumatism (EULAR) Sjogren’s Syndrome Disease Activity Index decreased from 8.8 (7.4) to 6.3 (6.6) (p = 0.0015) and EULAR Sjogren’s Syndrome Patient Reported Index from 6.4 (1.1) to 5.6 (2.0) (p = 0.0174). The mean dryness, fatigue and pain VAS varied from 7.8 (1.8) to 6.2 (2.9) (p = 0.0021), 6.9 (1.8) to 6.0 (2.2) (p = 0.0606) and 4.6 (2.6) to 4.7 (2.4) (p = 0.89), respectively. Salivary flow and Schirmer’s test did not change. The authors concluded that these encouraging results justified future randomized controlled trials of belimumab in a selected target population of pSS patients most likely to benefit from treatment.

In a single-arm, phase II clinical trial, Bishton et al (2013) evaluated the safety and activity of belimumab in 12 patients with Waldenstrom macroglobulinemia (WM). A total of 10 patients had stable disease with therapy, although no objective responses were seen. Correlative studies showed patients to have low or undetectable baseline serum levels of B-lymphocyte stimulator, with the administration of belimumab having no effect on B-cell numbers. The authors concluded that belimumab cannot be recommended as a single-agent therapy for the treatment of symptomatic WM, although further evaluation in combination with other agents would be justified.

Furuta and Jayne (2014) noted that the current standard therapy for anti-neutrophil cytoplasm antibody-associated vasculitis (AAV), high-dose glucocorticoid and cyclophosphamide followed by azathioprine, has improved the disease prognosis. However, there are still unmet needs. For example, reducing relapse risk and glucocorticoid toxicity; newer therapies are needed. These researchers stated that potential newer drugs are emerging following a better understanding of disease mechanisms and the availability of targeted therapies to B cells, T cells, pro-inflammatory cytokines and complement. Rituximab has proven efficacy in remission induction therapy for AAV, and 2 trials with rituximab as remission maintenance therapy are ongoing. Clinical trials evaluating mycophenolate mofetil as remission induction therapy, gusperimus, belimumab and complement factor C5a inhibition are also ongoing, and many other potential candidates are being investigated both clinically and experimentally. The authors concluded that B-cell therapy is now an established treatment in AAV and several other therapies are under evaluation. However, the unmet need in vasculitis therapy remains large and newer therapies either alone or in combination will need to both improve efficacy and permit reductions in glucocorticoid and immunosuppressive exposure.

Schwartz et al (2014) stated that renal involvement is a major cause of morbidity and mortality in SLE. These researchers provided an update on recent discoveries in the pathogenesis, diagnosis, and treatment of lupus nephritis. Localized long-lived plasma cells have been identified as playing an important role in lupus nephritis. In addition, the roles of aberrant expression of microRNAs and pro-inflammatory cytokines have been explored. Early diagnosis is important for effective treatment and multiple biomarkers
have been identified; however, none has been yet validated for clinical use. Biomarker panels may turn out to be more accurate than each individual component. Biologic agents for the treatment of lupus nephritis are being studied, including belimumab which was recently approved for non-renal SLE. Rituximab has not proven itself in large, placebo-controlled trials, although it is still being used in refractory cases of lupus nephritis. The authors concluded that lupus nephritis is a potentially devastating complication of SLE. Immune cells, cytokines, and epigenetic factors have all been recently implicated in lupus nephritis pathogenesis. These recent discoveries may enable a paradigm shift in the treatment of this complex disease, allowing the tailoring of treatment to target specific pathogenic mediators at specific points in time in the progression of disease.

In a review on "The future of uveitis treatment", Lin and colleagues (2014) listed belimumab as one of the emerging therapies for the treatment of uveitis. Furthermore, an UpToDate review on "Uveitis: Treatment" (Rosenbaum, 2014) does not mention belimumab as a therapeutic option.

Appendix

Benlysta is considered medically necessary for members who meet the following criteria:

1. Documented diagnosis of systemic lupus erythematosus based on ACR criteria, (see Table 1), and
2. Adult SLE patient with autoantibody-positive (anti-nuclear antibody, ANA) or anti-double stranded DNA (anti-dsDNA), and
3. At least one of the following 3 baseline measurement scores (see Table 2): SELENA-SLEDAI score, British Isles Lupus Assessment Group (BILAG) scores or Physician’s Global Assessment (PGA) score, and
4. Insufficient response to two (2) standard of care drug classes:
   a. Glucocorticoids (eg. prednisone, methylprednisolone, dexamethasone)
   b. Antimalarials (eg. hydroxychloroquine)
   c. Immunosuppressives (eg. azathioprine, methotrexate, mycophenolate, cyclosporine, cyclophosphamide, chlorambucil, nitrogen mustard)

Exclusion Criteria for Belimumab:

Individuals with severe active lupus nephritis (proteinuria greater than 6 g/24 hour or equivalent using spot urine protein to creatinine ratio, or serum creatinine greater than 2.5 mg/dL); or
Individuals with active nephritis; or
Individuals who require hemodialysis; or
Individuals who require high-dose prednisone greater than 100 mg/day within 90 days of day 0); or
Individuals with severe central nervous system (CNS) lupus (seizures, psychosis, organic brain syndrome, cerebrovascular accident, cerebritis or CNS vasculitis requiring therapeutic intervention within 60 days of day 0)

Table 1: American College of Rheumatology (ACR) Criteria for Classification of Systemic Lupus Erythematosus
The ACR criteria for classification of SLE (Table 1) are used to identify patients for clinical studies and requires 4 of 11 criteria at some point in their medical history for a person 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.

<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, sparing 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, y 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>Renal disorder</td>
<td>One of the following:</td>
</tr>
<tr>
<td></td>
<td>I. Persistent proteinuria &gt; 0.5gm/d or &gt;3+ if quantitation not performed</td>
</tr>
<tr>
<td></td>
<td>II. Cellular casts – may be red cell, hemoglobin, granular, tubular, or mixed</td>
</tr>
</tbody>
</table>

TABLE 1 – ACR Criteria
<table>
<thead>
<tr>
<th>Neurologic disorder</th>
<th>One of the following:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I. Seizures – in the absence of offending drugs or known metabolic derangement, e.g. uremia, ketoacidosis, or electrolyte imbalance</td>
</tr>
<tr>
<td></td>
<td>II. Psychosis – in the absence of offending drugs or known metabolic derangement, e.g., uremia, ketoacidosis, or electrolyte imbalance</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hematologic Disorder</th>
<th>One of the following:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I. Hemolytic anemia with reticulocytosis</td>
</tr>
<tr>
<td></td>
<td>II. Leukopenia - &lt;4,000/mm(^3) on ≥2 occasions</td>
</tr>
<tr>
<td></td>
<td>III. Lymphopenia - &lt;1,500/mm(^3) on ≥2 occasions</td>
</tr>
<tr>
<td></td>
<td>IV. Thrombocytopenia - &lt;100,000/mm(^3) in the absence of offending drugs</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Immunologic disorder</th>
<th>One of the following:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I. Anti-DNA: antibody to native DNA in abnormal titer</td>
</tr>
<tr>
<td></td>
<td>II. Anti-Sm: presence of antibody to Sm nuclear antigen</td>
</tr>
<tr>
<td></td>
<td>III. Positive finding of antiphospholipid antibodies based on:</td>
</tr>
<tr>
<td></td>
<td>A. Abnormal serum level of IgG or IgM anticardiolipin antibodies</td>
</tr>
<tr>
<td></td>
<td>B. A positive test result for lupus anticoagulant using a standard method</td>
</tr>
<tr>
<td></td>
<td>C. A false-positive test result for at least 6 months and confirmed by <em>Treponema pallidum</em> immobilization or fluorescent treponemal antibody absorption tests</td>
</tr>
</tbody>
</table>

| 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 |


**Table 2: Validated Scoring Instruments for Systemic Lupus Erythematosus**

The scoring measurements (Table 2) were used in the BENLYSTA phase III trials to detect clinically and meaningful responses to therapy.
<table>
<thead>
<tr>
<th>Instrument</th>
<th>Disease Variable Assessed</th>
<th>Disease Activity Category Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td>SELENA SLEDAI</td>
<td>24 weighted descriptors representing organ manifestations of SLE in past 10 days Flares Need for therapy</td>
<td>Range 0 to 105</td>
</tr>
<tr>
<td>BILAG</td>
<td>Individual organ manifestations of SLE in past 28 days Flares Score determined by physicians intention to treat 86 total items assessed</td>
<td>A = need for prednisone &gt; 20 mg/d or new immunosuppressives B = need for antimalarials, NSAIDs, or prednisone &lt; 20 mg/d C = stable, mild disease D = organ previously affected but not currently active E = no history of organ involvement</td>
</tr>
<tr>
<td>PGA</td>
<td>Global disease activity at a particular physician visit</td>
<td>Range 0 to 3 on a visual analog scale 10 cm in length 0 = none 1 = mild 2 = moderate 3 = severe</td>
</tr>
</tbody>
</table>


CPT Codes / HCPCS Codes / ICD-9 Codes

Other CPT codes related to the CPB:

86038
96365

**HCPCS codes covered if selection criteria are met:**

J0490

**Other HCPCS codes related to the CPB:**

J0390  Injection, chloroquine hydrochloride
J0456  Injection, azithromycin, 500 mg
J1020  Injection, methylprednisolone acetate, 20 mg
J1030  Injection, methylprednisolone acetate, 40 mg
J1094  Injection, dexamethasone acetate, 1 mg
J1100  Injection, dexamethasone sodium phosphate, 1 mg
J1700  Injection, hydrocortisone acetate, up to 25 mg
J1710  Injection, hydrocortisone sodium phosphate, up to 50 mg
J1720  Injection, hydrocortisone sodium succinate, up to 100 mg
J7312  Injection, dexamethasone, intravitreal implant, 0.1 mg
J7500  Azathioprine, oral, 50 mg
J7501  Azathioprine, parenteral, 100 mg
J7502  Cyclosporine, oral, 100 mg
J7506  Prednisone, oral, per 5 mg
J7509  Methylprednisolone oral, per 4 mg
J7515  Cyclosporine, oral, 25 mg
J7516  Cyclosporine, parenteral, 250 mg
J7517  Mycophenolate mofetil, oral, 250 mg
J7637  Dexamethasone, inhalation solution, compounded product, administered through dme, concentrated form, per milligram
J7638  Dexamethasone, inhalation solution, compounded product, administered through dme, unit dose form, per milligram
J8540  Dexamethasone, oral 0.25 mg
J8610  Methotrexate; oral, 0.25 mg
J9070  Cyclophosphamide, 100 mg [not covered when used in combination with Benlysta]
Q0144 Azithromycin dihydrate, oral, capsules/powder, 1 gram

**ICD-9 codes covered if selection criteria are met:**

710.0 Systemic lupus erythematosus

**ICD-9 codes not covered for indications listed in the CPB (not all-inclusive):**

273.3 Macroglobulinemia, Waldenstrom’s macroglobulinemia
289.81 Primary hypercoagulable state [anti-phospholipid antibody syndrome]
340 Multiple sclerosis
358.00 Myasthenia gravis without (acute) exacerbation
446.0 Polyarteritis nodosa [antibody-associated vasculitis]
446.4 Wegener’s granulomatosis [antibody-associated vasculitis]
710.2 Sicca syndrome
714.0 Rheumatoid arthritis
V42.0 Kidney replaced by transplant
V42.1 Heart replaced by transplant
V42.6 Lung replaced by transplant
V42.7 Liver replaced by transplant
V42.82 Peripheral stem cells replaced by transplant
V42.83 Pancreas replaced by transplant
V42.84 Intestines replaced by transplant
V45.11 Renal dialysis status

**The above policy is based on the following references:**