Introduction

The term “autoimmune disorders” refers to a number of conditions where a person’s immune system is activated against a part of their body. Many of these diseases are grouped together based on what part of the body is affected. The cells involved are usually lymph cells, and disease develops consistent with long standing inflammation. Common autoimmune disorders include certain types of arthritis, some skin diseases, inflammatory bowel diseases and others. This policy discusses treatment for the following autoimmune diseases: hidradenitis suppurativa, systemic lupus erythematosus (lupus), and pyoderma gangrenosum. The policy describes which drugs need to be pre-approved before they are covered by the plan.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs providers about when a service may be covered.

Policy Coverage Criteria

We will review specific intravenous (IV) and injectable drugs for medical necessity for all ages.
For those age 13 and older, we also will review the site of service for medical necessity. Site of service is defined as the location where the drug is administered, such as a hospital-based outpatient setting, an infusion center, a physician’s office, or at home.

**Drugs subject to site of service review addressed in this policy are:**

- Benlysta® (belimumab)
- Remicade® (infliximab)
- Inflectra® (infliximab-dyyb)
- Renflexis® (infliximab-abda)

**Note:** Medications listed in this policy may also be subjected to quantity limits per the FDA labeled dosing.

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**Click on the links below to be directed to the related medical necessity criteria:**

- Behcet’s Disease
- Giant Cell Arteritis
- Hidradenitis Suppurativa (HS)
- Pyoderma Gangrenosum

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<table>
<thead>
<tr>
<th>Site of Service Administration</th>
<th>Medical Necessity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medically necessary sites of service</td>
<td>IV infusion therapy of various medical or biologic agents will be covered in the most appropriate, safe and cost effective site:</td>
</tr>
<tr>
<td>• Physician’s office</td>
<td>• These are the preferred <strong>medically necessary</strong> sites of service for specified drugs.</td>
</tr>
<tr>
<td>• Infusion center</td>
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<tr>
<td>• Home infusion</td>
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</tr>
<tr>
<td>Site of Service Administration</td>
<td>Medical Necessity</td>
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<tr>
<td>--------------------------------</td>
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</tr>
<tr>
<td>Hospital-based outpatient setting</td>
<td>IV infusion therapy of various medical or biologic agents will be covered in the most appropriate, safe and cost-effective site.</td>
</tr>
<tr>
<td>• Outpatient hospital IV infusion department</td>
<td><strong>This site is considered medically necessary for the first 90 days for the following:</strong></td>
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<tr>
<td>• Hospital-based outpatient clinical level of care</td>
<td>• The initial course of infusion of a pharmacologic or biologic agent</td>
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<td></td>
<td><strong>OR</strong></td>
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<tr>
<td></td>
<td>• Re-initiation of an agent after 6 months or longer following discontinuation of therapy*</td>
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<tr>
<td></td>
<td><strong>Note:</strong> This does not include when standard dosing between infusions is 6 months or longer</td>
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</tbody>
</table>

This site is considered medically necessary when there are no outpatient infusion center within 50 miles of the patient’s home and there is no contracted home infusion agency that will travel to their home, or a hospital is the only place that offers infusions of this drug.

This site is considered medically necessary only when the patient has a clinical condition which puts him or her at increased risk of complications for infusions, including any ONE of the following:

- Known cardiac condition (e.g., symptomatic cardiac arrhythmia) or pulmonary condition (e.g., significant respiratory disease, serious obstructive airway disease, \%FVC ≤ 40%) that may increase the risk of an adverse reaction
- Unstable renal function which decreases the ability to respond to fluids
- Difficult or unstable vascular access
- Acute mental status changes or cognitive conditions that impact the safety of infusion therapy
<table>
<thead>
<tr>
<th>Site of Service Administration</th>
<th>Medical Necessity</th>
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</thead>
<tbody>
<tr>
<td>Hospital-based outpatient setting</td>
<td>• A known history of severe adverse drug reactions and/or anaphylaxis to prior treatment with a related or similar drug</td>
</tr>
<tr>
<td>• Outpatient hospital IV infusion department</td>
<td>These sites are considered not medically necessary for infusion and injectable therapy services of various medical and biologic agents when the site-of-service criteria in this policy are not met.</td>
</tr>
<tr>
<td>• Hospital-based outpatient clinical level of care</td>
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</table>

<table>
<thead>
<tr>
<th>Agent</th>
<th>Medical Necessity</th>
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</thead>
<tbody>
<tr>
<td><strong>Hidradenitis Suppurativa (HS)</strong></td>
<td></td>
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<tr>
<td><strong>First-line TNF-α Antagonists</strong></td>
<td></td>
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<tr>
<td>• Humira® (adalimumab)</td>
<td>Humira® (adalimumab) may be considered medically necessary as the first-line agent in the treatment of hidradenitis suppurativa in patients 12 years of age and older when the patient has a documented diagnosis of this condition.</td>
</tr>
<tr>
<td><strong>Systemic Lupus Erythematosus (SLE)</strong></td>
<td></td>
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<tr>
<td><strong>Anti-CD20</strong></td>
<td>See policy 5.01.556 Rituximab: Non-oncologic and Miscellaneous Uses</td>
</tr>
<tr>
<td>• Rituxan® (rituximab)</td>
<td></td>
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<tr>
<td>• Ruxience™ (rituximab-pvvr)</td>
<td></td>
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<tr>
<td>• Truxima® (rituximab-abbs)</td>
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<tr>
<td><strong>BLyS Inhibitors</strong></td>
<td>Benlysta® (belimumab) IV is subject to review for site of service administration.</td>
</tr>
</tbody>
</table>
| **Benlysta® (belimumab) IV** | Benlysta® (belimumab) IV may be considered medically necessary in the treatment of patients aged 5 years and older with active, autoantibody-positive SLE when both of the following conditions are met:

• The patient has a diagnosis of SLE confirmed using either the American College of Rheumatology (ACR) or Systemic Lupus International Collaborating Clinics (SLICC) criteria. |

AND |
<table>
<thead>
<tr>
<th>Agent</th>
<th>Medical Necessity</th>
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</table>
| Benlysta® (belimumab) SC | Benlysta® (belimumab) SC may be considered medically necessary in the treatment of adult patients with active, autoantibody-positive SLE when both of the following conditions are met:  
- The patient has a diagnosis of SLE confirmed using either the American College of Rheumatology (ACR) or Systemic Lupus International Collaborating Clinics (SLICC) criteria.  
AND  
- The patient has failed an adequate trial of standard induction therapy with mycophenolate, cyclophosphamide, azathioprine, or immunosuppressant, plus a corticosteroid. |

**Pyoderma Gangrenosum**

**First-line Agents**

**TNF-α Antagonists**  
- Humira® (adalimumab)  
- Enbrel® (etanercept)  

Humira® (adalimumab) or Enbrel® (etanercept) may be considered medically necessary as the first-line agent in the treatment of pyoderma gangrenosum when:  
- The patient has not responded to one standard non-biologic therapy (eg, oral corticosteroids, systemic cyclosporine, topical tacrolimus, etc.)

**Second-line Agents**

**TNF-α Antagonists**  
- Remicade® (infliximab)  

Remicade® (infliximab) is subject to review for site of service administration.  

Remicade® (infliximab) may be considered medically necessary as a first-line agent in the treatment of pyoderma gangrenosum when:  
- The patient has not responded to one standard non-biologic therapy (eg, oral corticosteroids, systemic cyclosporine, topical tacrolimus, etc.)

Inflectra® (infliximab-dyyb) and Renflexis® (infliximab-abda) are subject to review for site of service administration.
### Agent Medical Necessity

- **Renflexis® (infliximab-abda)**
  Inflectra® (infliximab-dyyb) and Renflexis® (infliximab-abda) may be considered medically necessary as a second-line agent in the treatment of pyoderma gangrenosum when:
  - The patient has not responded to one standard non-biologic therapy (e.g., oral corticosteroids, systemic cyclosporine, topical tacrolimus, etc.)
  AND
  - The patient has had an inadequate response or intolerance to Remicade® (infliximab)

### Uveitis

#### TNF-α Antagonists
- **Humira® (adalimumab)**
  Humira® (adalimumab) may be considered medically necessary as the first-line agent in the treatment of non-infectious intermediate uveitis, posterior uveitis, or panuveitis in adults and children 2 years of age and older when the patient has a documented diagnosis of one of these conditions.

### Giant Cell Arteritis

#### IL-6 Antagonist
- **Actemra® (tocilizumab) SC**
  Actemra® (tocilizumab) may be considered medically necessary as the first-line agent in the treatment of adult patients with giant cell arteritis.

### Behcet’s Disease

#### Phosphodiesterase 4 (PDE4) inhibitor
- **Otezla® (apremilast) Oral**
  Otezla® (apremilast) may be considered medically necessary for the treatment of adult patients with oral ulcers associated with Behcet’s Disease.

### Agent Investigational

- **As listed**
  All other uses of the above-named agents for conditions not outlined in this policy or in related policies are considered investigational.
### Length of Approval

<table>
<thead>
<tr>
<th>Approval</th>
<th>Criteria</th>
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<tbody>
<tr>
<td>Initial authorization</td>
<td>All drugs listed in policy may be approved up to 12 months.</td>
</tr>
<tr>
<td>Re-authorization criteria</td>
<td>Future re-authorization of all drugs listed in policy may be approved up to 12 months as long as the drug-specific coverage criteria are met and chart notes demonstrate that the patient continues to show a positive clinical response to therapy.</td>
</tr>
</tbody>
</table>

### Documentation Requirements

The patient’s medical records submitted for review for all conditions should document that medical necessity criteria are met. The record should include the following:

- Office visit notes that contain the diagnosis, relevant history, physical evaluation and medication history

### Coding

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>J0490</td>
<td>Injection, belimumab (Benlysta®), 10 mg</td>
<td></td>
</tr>
<tr>
<td>J0717</td>
<td>Injection, certolizumab pegol (Cimzia®), 1 mg (code may be used for Medicare when drug administered under the direct supervision of a physician, not for use when drug is self-administered)</td>
<td></td>
</tr>
<tr>
<td>J1438</td>
<td>Injection, etanercept (Enbrel®), 25mg (code may be used for Medicare when drug administered under the direct supervision of a physician, not for use when drug is self-administered)</td>
<td></td>
</tr>
<tr>
<td>J1745</td>
<td>Injection, infliximab (Remicade®), 10mg</td>
<td></td>
</tr>
<tr>
<td>J3262</td>
<td>Injection, tocilizumab, 1 mg (Actemra®)</td>
<td></td>
</tr>
<tr>
<td>Q5103</td>
<td>Injection, infliximab-dyyb, biosimilar, (Inflectra®), 10 mg</td>
<td></td>
</tr>
<tr>
<td>Q5104</td>
<td>Injection, infliximab-abda, biosimilar, (Renflexis®), 10 mg</td>
<td></td>
</tr>
<tr>
<td>Q5109</td>
<td>Injection, infliximab-qbtix, biosimilar, (ixifi), 10 mg</td>
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</tbody>
</table>

**Note:** CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).
Consideration of Age

Age limits specified in this policy are determined according to FDA-approved indications, where applicable.

For site of service for medical necessity the age described in this policy is 13 years of age or older. Site of service is defined as the location where the drug is administered, such as a hospital-based outpatient setting, an infusion center, a physician's office, or at home. The age criterion for site of service for medical necessity is based on the following: Pediatric patients are not small adults. Pediatric patients differ physiologically, developmentally, cognitively, and emotionally from adult patients, and vary by age groups from infancy to teen. Children often require smaller doses than adults, lower infusion rates, appropriately sized equipment, the right venipuncture site determined by therapy and age, and behavioral management during administration of care. Specialty infusion training is therefore necessary for pediatric IV insertions and therapy. Due to pediatrics unique physiology and psychology, site of service review is limited to patients above the age of 13.

Evidence Review

Miscellaneous Autoimmune Diseases

TNF inhibitors, rituximab and various other agents have been used off-label to treat a variety of autoimmune diseases. Most of this use represents significant unmet medical needs for chronic diseases with few treatment options.

Hidradenitis Suppurativa

Hidradenitis Suppurativa (HS) is an inflammatory skin disease affecting an estimated 1 to 4% of the world population. The main features of HS include painful and chronically recurring, deep-seated follicular nodules, papules, pustules, and abscesses, scarring, sinus tracts, and recurrent
discharge. The area’s most commonly affected are the under the arms, groin, buttocks, and under the breasts. The disease is variable and recurrent. It may occur as solitary or multiple lesions in one area, or in many areas. In more severe cases, there may be large areas of skin affected by recurrent, draining lesions.

The U.S. Food and Drug Administration (FDA) approved Humira® (adalimumab) to treat patients with HS.

Two randomized, double-blind, placebo-controlled studies (Studies HS-I and II) evaluated the safety and efficacy of Humira in a total of 633 adult subjects with moderate to severe hidradenitis suppurativa (HS) with Hurley Stage II or III disease and with at least 3 abscesses or inflammatory nodules. In both studies, subjects received placebo or Humira at an initial dose of 160 mg at Week 0, 80 mg at Week 2, and 40 mg every week starting at Week 4 and continued through Week 11. Subjects used topical antiseptic wash daily. Concomitant oral antibiotic use was allowed in Study HS-II.

Both studies evaluated Hidradenitis Suppurativa Clinical Response (HiSCR) at Week 12. HiSCR was defined as at least a 50% reduction in total abscess and inflammatory nodule count with no increase in abscess count and no increase in draining fistula count relative to baseline (see Table below). Reduction in HS-related skin pain was assessed using a Numeric Rating Scale in patients who entered the study with an initial baseline score of 3 or greater on a 11 point scale.

In both studies, a higher proportion of Humira than placebo-treated subjects achieved HiSCR (see Table 1 below).

Table 1. Efficacy Results at 12 Weeks in Subjects with Moderate to Severe Hidradenitis Suppurativa

<table>
<thead>
<tr>
<th></th>
<th>HS Study I</th>
<th></th>
<th>HS Study II*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Humira 40 mg Weekly</td>
<td>Placebo</td>
</tr>
<tr>
<td>Hidradenitis Suppurativa Clinical Response (HiSCR)</td>
<td>N=154, 40 (26%)</td>
<td>N=153, 64 (42%)</td>
<td>N=163, 45 (28%)</td>
</tr>
</tbody>
</table>

*19.3% of subjects in Study HS-II continued baseline oral antibiotic during the study.

In both studies, from Week 12 to Week 35 (Period B), subjects who had received Humira were re-randomized to 1 of 3 treatment groups (Humira 40 mg every week, Humira 40 mg every
other week, or placebo). Subjects who had been randomized to placebo were assigned to receive Humira 40 mg every week (Study HS-I) or placebo (Study HS-II).

During Period B, flare of HS, defined as ≥25% increase from baseline in abscesses and inflammatory nodule counts and with a minimum of 2 additional lesions, was documented in 22 (22%) of the 100 subjects who were withdrawn from Humira treatment following the primary efficacy time point in two studies.

**Lupus – Systemic Lupus Erythematosus (SLE)**

Systemic lupus erythematosus (SLE) is a chronic, complicated, progressive autoimmune disease impacting multiple organ systems. It is a condition characterized by auto-reactive b-cells. Autoantibody production from such abnormal b lymphocyte function leads to chronic inflammation and cellular, tissue and organ damage. Diverse in presentation, patients with SLE experience mild to life-threatening manifestations and unpredictable clinical course of exacerbations and remissions. As symptoms are non-specific, the identification of SLE is often-times delayed. It has been reported that patients visit a mean of three different physicians and an average of 4 years after the onset of symptoms before a correct diagnosis is reached.

The mucocutaneous (rash), articular (arthritis), serosal (pleuritis, pericarditis), renal (proteinuria) and neurologic (seizures, psychosis) clinical features, as well as hematologic and immunologic laboratory findings, incorporated in the American College of Rheumatology SLE diagnosis classification criteria reflects the heterogeneity of the disease. Most commonly involved organs include the skin, musculoskeletal, renal, nervous, cardiovascular and pulmonary systems. Over 75% of SLE patients have debilitating, generally non-fatal mucocutaneous (rash) and musculoskeletal involvement (arthritis). A smaller SLE population (50%-66%) is afflicted with renal disorders, and is associated with poorer outcome and mortality. About 2/3 of SLE patients also present with varying severity of neuropsychiatric manifestations ranging from mood disorders, anxiety, psychosis to seizures. Other less common but serious manifestations include serositis (16 to 64%), neurological disorders (9 to 36%), and immune-mediated cytopenia’s (4 to 43%). Depression is common among people with chronic autoimmune disease. Overall, SLE patients have a 2-5 times greater mortality rate.

As endogenous female sex hormone is identified to have a role in SLE development, SLE is found primarily in women (90% of SLE population are female, 6-10 female:1 male), typically 15-44 years of age. In the US, more than 300,000 people have SLE and an annual incident rate of 15,000. 4 million people are impacted worldwide.
While SLE patients have at least twice the mortality risk relative to the general population, survival rate at 15 years improved dramatically from 50% in the 1950s to currently greater than 80%. Most common causes of death are cardiovascular disease, infections, renal disease and complications due to SLE disease activity.

In addition to gender, ethnicity has an influence on the development of SLE. Mestizo, indigenous Americans, Blacks and Asians have more severe SLE disease and poorer clinical progression. Blacks are three times more likely than Caucasians to have SLE. Asian and African American SLE patients develop renal disease more frequently than those of European descent (60-70%, 50%, 20-30%, respectively).

SLE is characterized by auto-reactive B-cells. Autoantibody production from such abnormal B lymphocyte function leads to chronic inflammation. Autoantibody complex, cytokines and complement activation represent mediators of tissue damage in SLE patients. Anti-nuclear antibody (ANA) is found present in more than 90% of patients. Those positive are more likely to have active lupus associated with B cell dysfunction. Anti-dsDNA, a type of ANA, is one of the diagnosis criteria established by the American College of Rheumatology and is monitored as gauge of SLE disease response to treatment. Consistent with existing pathophysiology, inhibition of BLyS, an endogenous protein responsible for B-cell homeostasis, decreases autoreactive B-cell activity and serological changes. Transgenic animals overexpressing BLyS have lupus-like syndrome, increased immunoglobulins and immune complex depositions. BLyS is also found elevated in human autoimmune diseases such as rheumatoid arthritis, multiple sclerosis and Sjögren's.

Most patients present with generalized symptoms of fatigue, fever, anorexia, weight loss, photosensitivity, malar rash, oral ulcers, arthralgia and hair loss. Incompletely controlled SLE can progress to end-stage organ involvement; SLE activity of 60% of SLE patients is found to worsen within 2-7 years of diagnosis. Irreversible cellular and tissue damages can accumulate to result in life-threatening renal, cardiac, pulmonary, CNS and hematological system toxicities. The subsequent development of pleuritis, pericarditis, stroke, seizure, nephritis, vasculitis, anemia, thrombocytopenia and other blood dyscrasias present significant mortality and morbidity risks.

Aside from these autoimmune mediated disease manifestations, SLE patient are in high risk for infections of the respiratory and urinary systems, cardiovascular diseases, hematological and solid tumors, maternal and fetal morbidity and mortality (spontaneous abortions, pre-eclampsia, intrauterine growth impairment, premature birth). Most common causes of death are infections, renal disease, cardiovascular disease and complications due to SLE disease activity.

The current SLE standard of care is similar across the world. Treatment of mild-to-moderate symptoms involves the use of non-steroidal anti-inflammatory drugs (NSAIDs), antimalarial
drugs such as hydroxychloroquine and corticosteroids such as prednisone and its equivalent. For life-threatening manifestations such as the renal, CNS, cardiovascular and pulmonary systems, aggressive single or combination of treatments with high dose corticosteroids and immunosuppressive agents such as cyclophosphamide, azathioprine, methotrexate and mycophenolate is used. Corticosteroids, hydroxychloroquine and aspirin have FDA approved SLE indications.

Particularly for patients with active and life-threatening disease activity, SLE remains an unmet medical disease. The very treatments used to alleviate lupus symptoms have poor tolerability and short and long term morbidity risks. Ones used for mild/mod SLE flares involves nonspecific immune system suppression. Aggressive treatments such as cyclophosphamide is associated with gonadal toxicity, whereas high dose corticosteroids (>7.5 mg/day, cumulative doses >365g) can lead to cataracts, osteoporosis, metabolic disorders, increased infections, edema, weight gain and hyperlipidemia. This is especially concerning as SLE patients tend to be young women of child bearing age, have lower immune system and greater cardiovascular risks due to the nature of the underlying autoimmune disease. Currently there is no approved SLE treatment shown to prolong survival or reverse the course of the disease.

**Benlysta® (belimumab)**

Benlysta® (belimumab) is an FDA-approved 147kDa, recombinant fully human IgG1λ monoclonal antibody. It targets a novel pathway to potentially treat SLE by binding to soluble, endogenous human B-lymphocyte stimulator BLYS (also known as B cell activating factor or BAFF, TALL-1, THANK, TNFSF13B, zTNF4). The binding inhibits BLYS biological activity of B-cell selection, survival, differentiation and eventual antibody formation of native, activated plasmacytoid and plasma cells.

The efficacy of belimumab was studied in two Phase III trials. SLE Responder Index (SRI) response at 52 weeks, the primary endpoint, was met for belimumab 10 mg/kg treatment arm in both BLISS 52 [1.83 OR (1.30-2.59), p=0.0006] and BLISS76 [1.52 OR (1.07-2.15), p=0.0207]. Overall, secondary endpoints of reduction in severe flare, steroid use, autoantibodies, B-cell subsets, normalization of complement levels and improvement in quality of life were also achieved. 66% of the U.S. Food and Drug Administration (FDA) Arthritis Advisory Committee (10 out of 15) felt the clinical data provide support of efficacy. Concerns were cited over the lack of study consistency within and between the phase 3 studies, lack of statistical significance for some populations and the exclusion of SLE patients with severe renal or central nervous system diseases. The representative nature of the SLE patients sampled was also questioned.
The two Phase III studies were set-up nearly identically, though differences in baseline demographics, serological activity, geographical location and concurrent SLE medication use necessitate their separate analyses. Bliss 76 was conducted in North America and Europe, with 70% Caucasian and 14% African American. Relative to BLISS 52, BLISS 76 had a lower baseline SLE activity (less of SS score >=10, proteinuria>= 2g/24 hours, 1A or 2B BILAG, auto-antibodies, much less prescribed corticosteroid, while using greater NSAIDS and immunosuppressive agents). The data from BLISS 76 clinical trial was less convincing, with its more narrow incremental benefit of belimumab over placebo in SRI response, steroid use and SLE flare reduction, lack of efficacy for African American groups, and later onset of significant SS score improvement (32 weeks versus 16 weeks in BLISS 52). With the exception of African American groups, the evidence from BLISS 52 clinical trial was stronger, more robust and consistent across different ethnicities. A lower number of BLISS 52 participants receiving 10mg/kg belimumab required an increase of corticosteroids. Reduction in flares and prolongation to first flare were seen only in this ex-U.S.-conducted study.

For both studies, disease manifestation resolution often seen in organ systems were those commonly involved at baseline: mucocutaneous (rash, oral ulcers, alopecia), immunologic (serological measures of disease activity, antids-DNA and complements) and musculoskeletal (arthritis). SLE activity reduction was also observed with the vascular (vasculitis) and central nervous system (lupus headache), both systems of which were less commonly involved at study initiation. However, resolution of similarly less frequently-involved hematology abnormalities and fever was not observed in the belimumab group. The statistically significant difference in improvement from baseline as benchmarked by SRI response was driven largely by improvement of the mucocutaneous and musculoskeletal systems, and not organ systems more associated with poor SLE outcome and mortality (kidneys, central nervous system, blood vessels). Observations of these serious organ manifestations were too uncommon to assess treatment effects.

Subgroup analyses revealed a lack demonstrated efficacy in African American subjects in both Phase III studies, which contradicted the positive treatment response previously observed in LBS02 Phase II trial. Similarly, Native Americans were found more associated with favorable disease activity reduction in BLISS 52 but not its counterpart trial. There was some geographical dependence, as participants from U.S. and Canada had smaller treatment effect compared to some other regions. Since belimumab is to be administered chronically, durability and onset of response are of concern. Of note, differences in efficacy endpoint at the conclusion of BLISS 76 were no longer statistically significant between treatment arms [PLO 32%, 10mg/kg 39%, 1.3 (0.9, 1.9), p=0.13], which was a drop from PLO 34%, 10mg/kg 43% 1.5 (1.07, 2.15), p=0.0207 in the preceding 24 weeks. Dose-response was not consistent; throughout the studies, 1mg/kg was noticed at times to be more, or just as, effective as the more potent proposed formulation.
Patients with severe renal or central nervous system (CNS) diseases were not evaluated and therefore efficacy not known. A disclaimer to this effect was included in the final approved product label.

As safety data were pooled from the three intravenous belimumab clinical studies (LBS02, BLISS 52 and BLISS76) in an attempt to generate a sufficiently large sample of rare events, the ability to detect safety trend concerning specific ethnicity and geological populations was lost. Overall, headache, upper respiratory tract infection and arthralgia were some of the common adverse events experienced by belimumab participants. Pyrexia was the most reported serious adverse event. The investigational drug was found associated with greater risk of infection, mortality and psychiatric events ranging from depression, suicidal ideation to suicide. Notably, no such neuropsychiatric adverse events were seen in those receiving only SLE standard therapy. Malignancy and hypersensitivity rates were comparable to the placebo group. While belimumab has safety signals, its safety profile is favorable and relatively minor compared to the side effects experienced by those on current SLE standard-of-care. 14 of the 15 Advisory Committee members agreed that the clinical data provided adequate safety evidence.

In Trial 4 the safety and efficacy of Benlysta IV was evaluated in an international, randomized, double-blind, placebo-controlled, 52-week, pharmacokinetics (PK), efficacy and safety study conducted in 93 pediatric patients with a clinical diagnosis of SLE according to the American College of Rheumatology classification criteria. Patients had active SLE disease, defined as a SELENA-SLEDAI score ≥6 and positive autoantibodies at screening as defined in the adult trials. Patients were on a stable SLE treatment regimen (standard of care) and had similar inclusion and exclusion criteria as in the adult studies. The median age was 15 years (range: 6 to 17). The majority (95%) of patients were female. More than 50% of patients had 3 or more active organ systems involved at baseline. The most common active organ systems at baseline based on SELENA-SLEDAI were mucocutaneous (91%), immunologic (74%), and musculoskeletal (73%). Overall, 19% of pediatric patients had some degree of renal activity and less than 7% had activity in the cardio-respiratory, hematologic, CNS or vascular systems. Randomization into age-related treatment cohorts was stratified by screening SELENA-SLEDAI scores (6 to 12 vs >13) and age (5 to 11 years vs 12 to 17 years).

The primary efficacy endpoint was the SLE Responder Index (SRI-4) at Week 52. There was a numerically higher proportion of pediatric patients achieving a response in SRI-4 and its components in pediatric patients receiving Benlysta IV plus standard therapy compared with placebo plus standard therapy.

At baseline, 95% of pediatric patients were receiving prednisone. Among those pediatric patients, 20% of pediatric patients receiving Benlysta IV plus standard therapy reduced their
average prednisone dose by at least 25% per day during Weeks 44 through 52 compared with 21% of pediatric patients on placebo plus standard therapy.

In Trial 4, the probability of experiencing a severe SLE flare, as measured by the modified SELENA-SLEDAI Flare Index, excluding severe flares triggered only by an increase of the SELENA-SLEDAI score to >12, was calculated. The proportion of pediatric patients reporting at least one severe flare during the study was numerically lower in pediatric patients receiving Benlysta IV plus standard therapy (23%) compared with those receiving placebo plus standard therapy (43%). Pediatric patients receiving Benlysta IV 10 mg/kg plus standard therapy had a 62% lower risk of experiencing a severe flare during the 52 weeks of observation, relative to the placebo plus standard therapy group. Of the pediatric patients experiencing a severe flare, the median time to the first severe flare was 160 days in pediatric patients receiving Benlysta IV plus standard therapy compared with 82 days in pediatric patients receiving placebo plus standard therapy.

**Pyoderma Gangrenosum**

Pyoderma gangrenosum is an inflammatory disease with dermatologic manifestations including painful ulcerations with erythematous borders. It is presumed to be autoimmune in origin, though the mechanism is not well understood. Lesions usually develop at sites of minor skin injury, usually on the lower extremities. These lesions can grow in size and become necrotic. Underlying fasciitis may occasionally develop from them. Some patients develop pustular, bullous or vegetative lesions. Other common sites are colostomies and paraneoplastic lesions in patients with hematologic malignancies. Progress of the lesions is highly variable, and patient response to treatment is heterogeneous. Obesity, diabetes or edema may be contributing factors.

Due to the infrequent occurrence and heterogeneity of pyoderma gangrenosum, the treatment approach is empiric and patient-specific. First-line options include topical tacrolimus, nicotine, and 5-ASA, systemic corticosteroids and immunosuppressant agents such as azathioprine, cyclosporine, methotrexate and mycophenolate. When these approaches fail, biologic therapy is usually tried. Successful treatment with TNF inhibitors (etanercept, adalimumab, infliximab) has been reported. Response to ustekinumab and various investigational interleukin inhibitors has also been reported. Surgical management is another option.
**Wegener’s Granulomatosis and Microscopic Polyangiitis**

Wegener’s granulomatosis (WG) is an autoimmune vasculitis that may affect various internal organs and can be potentially life-threatening. Symptoms vary and can mimic a variety of other diseases, making it difficult to diagnose. These include rhinitis, glomerulonephritis, pulmonary nodules and hemorrhage, neuropathies, gastrointestinal symptoms and various other inflammatory manifestations. The disease can occur at any age, usually in adults.

WG can be recognized by the distinctive triad of granulomatous inflammation, necrosis, and vasculitis of the respiratory tract. Vasculitis in other regions is also common. It can follow a varied clinical course that is strongly influenced by treatment. Untreated, generalized WG is usually lethal. Historically, treatment with immunosuppressants has been used. Glucocorticoids and cyclophosphamide have been a standard therapy, but this is limited by cyclophosphamide toxicity. If remission is achieved, less toxic agents such as azathioprine may be employed for maintenance.

The U.S. Food and Drug Administration (FDA) has approved rituximab in combination with glucocorticoids, to treat patients with WG and microscopic polyangiitis (MPA). Both of these diseases affect people of all ages and ethnicities, and both genders. The causes of these disorders are unknown, and both are considered orphan diseases because they each affect less than 200,000 people in the United States.

**Giant Cell Arteritis**

Giant cell arteritis (GCA) is an inflammation of the lining of the arteries. It affects the arteries in the head, especially those in the temples. Temporal arteritis is another name for this disease. GCA frequently causes headaches, scalp tenderness, jaw pain, and vision problems.

The safety of subcutaneous Actemra (tocilizumab) has been studied in one Phase III study (WA28119) with 251 GCA patients. The total patient years duration in the Actemra GCA all exposure population was 138.5 patient years during the 12-month double blind, placebo-controlled phase of the study. The overall safety profile observed in the Actemra treatment groups was generally consistent with the known safety profile of Actemra. There was an overall higher incidence of infections in GCA patients relative to RA patients. The rate of infection/serious infection events was 200.2/9.7 events per 100 patient years in the Actemra weekly group and 160.2/4.4 events per 100 patient years in the Actemra every other week group as compared to 156.0/4.2 events per 100 patient years in the placebo + 26 week prednisone taper and 210.2/12.5 events per 100 patient years in the placebo + 52 week taper groups.
2019 Update

Reviewed prescribing information and conducted literature search for all drugs listed in policy. Updated criteria for Benlysta® (belimumab) IV for use in patients aged 5 years and older.

References

## History

<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>07/01/16</td>
<td>New policy approved June 14, 2016, add to Prescription Drug section. Policy information on drug treatment for miscellaneous autoimmune diseases extracted from 5.01.550. Medical necessity review criteria for site of service IV therapy added.</td>
</tr>
<tr>
<td>10/01/16</td>
<td>Interim Update, approved September 13, 2016: inclusion of a new indication for Humira; changing criteria for Benlysta (defining &quot;adequate&quot; trial of previous therapies).</td>
</tr>
<tr>
<td>11/01/16</td>
<td>Interim review, approved October 11, 2016. Clarified age criteria language indicating that site of service review is applicable to only those age 13 and older; drug criteria review applies to all ages. Coding update, added HCPCS QS102.</td>
</tr>
<tr>
<td>07/01/17</td>
<td>Annual review, approved June 13, 2017. Added coverage criteria for Actemra® in the setting of giant cell arteritis, added HCPCS code J3262. Formatting update; added hyperlinks to Medical Necessity criteria sections.</td>
</tr>
<tr>
<td>08/15/17</td>
<td>Interim Review, approved August 15, 2017. Added Benlysta SC.</td>
</tr>
<tr>
<td>09/01/17</td>
<td>Interim review, approved August 15, 2017. Added Infliximab-abda (Renflexis) to coverage criteria and coding section. Clarified pyoderma gangrenosum first-line/second-line treatment.</td>
</tr>
<tr>
<td>11/01/17</td>
<td>Interim Review, approved October 3, 2017. Clarified site of service exception criterion related to access: There is no outpatient infusion center within 50 miles of the patient’s home and there is no contracted home infusion agency that will travel to their home, or a hospital is the only place that offers infusions of this drug. Removed HCPCS codes J3490 and J3590.</td>
</tr>
<tr>
<td>02/14/18</td>
<td>Interim Review, approved February 13, 2018. Update hospital based outpatient coverage from 30 days to 90 days.</td>
</tr>
<tr>
<td>04/01/18</td>
<td>Coding update; added new HCPCS codes Q5103 and Q5104 (effective 4/1/18), noted that Q5102 terminated 4/1/18.</td>
</tr>
<tr>
<td>07/01/18</td>
<td>Annual Review, approved June 22, 2018. Dosage and quantity limit prescribing table was removed. Two related medical policies were added in related medical policy section.</td>
</tr>
<tr>
<td>11/01/18</td>
<td>Minor update, the Site of Service criteria was updated for clarity.</td>
</tr>
<tr>
<td>12/01/18</td>
<td>Interim Review, approved November 21, 2018. Updated pediatric indications for Humira: uveitis and hydradenitis.</td>
</tr>
<tr>
<td>Date</td>
<td>Comments</td>
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<td>------------</td>
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<tr>
<td>01/01/19</td>
<td>Coding update, added new HCPCS code Q5109 (new code effective 1/1/19).</td>
</tr>
<tr>
<td>04/01/19</td>
<td>Coding update, removed HCPCS code Q5102 as it terminated 4/1/18.</td>
</tr>
<tr>
<td>09/01/19</td>
<td>Interim Review, approved August 22, 2019. Added criteria for Otezla (apremilast) for Behcet’s Disease.</td>
</tr>
<tr>
<td>01/01/20</td>
<td>Interim Review, approved December 17, 2019, effective for dates of service on or after April 3, 2020, following provider notification.   Added Ruxience (rituximab-pvvr) with Rituxan.</td>
</tr>
</tbody>
</table>

**Disclaimer:** This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2020 Premera All Rights Reserved.

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Email AppealsDepartmentinquiries@Premera.com

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