Medication Policy Manual

Policy No: dru248

Topic: Benlysta®, belimumab

Date of Origin: May 13, 2011

Committee Approval Date: April 14, 2017

Next Review Date: August 2018

Effective Date: August 14, 2017

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medication policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Belimumab (Benlysta®) is a monoclonal antibody that is intravenously or subcutaneously administered, and used in the treatment of adult patients with active, auto-antibody positive systemic lupus erythematosus who are receiving standard therapy. It works by lessening the body's immune response.

Policy/Criteria

I. Most contracts require prior authorization approval of belimumab prior to coverage. Belimumab may be considered medically necessary in adult patients when criteria A, B, C, D, and E listed below, are met.

A. [For the intravenous (IV) formulation only] Site of care administration requirements are met. [refer to OmedaRx Medication Policy Manual, Site of Care Review, dru408]

AND

B. There is a diagnosis of active, systemic lupus erythematosus (SLE) requiring treatment of the mucocutaneous (skin) and/or musculoskeletal organ system.

AND

C. The patient is auto-antibody positive (seropositive), defined as meeting either criterion 1 or 2 below:

1. Antinuclear antibody (ANA) positive (titer ≥ 1:80).

OR

2. Anti-double-stranded DNA (anti-dsDNA) positive (concentration ≥ 30 IU/mL).

AND

D. Clinical documentation of functional impairment due to poor SLE control, which may include (but is not limited to) documentation of limitation of activities of daily living (ADLs) due to pain, impaired ambulation, or missing school or work.

AND

E. Patient is currently on therapy for systemic lupus erythematosus and criteria 1, 2 and 3 listed below are met.

1. Patient requires daily use of oral corticosteroids, unless contraindicated, or previously ineffective or not tolerated.

AND

2. Previous treatment courses of at least 12 weeks each with 2 or more of the following have been ineffective: chloroquine, hydroxychloroquine, methotrexate, azathioprine, cyclophosphamide OR mycophenolate mofetil, unless all are contraindicated or not tolerated.

AND

3. Patient is not currently on intravenously administered cyclophosphamide.

II. Administration, Quantity Limitations and Authorization Period

A. OmedaRx does <u>not</u> consider intravenous (IV) belimumab to be a self-administered medication.

B. OmedaRx considers subcutaneous (SC) belimumab to be a self-administered

medication.

C. When prior authorization is approved, belimumab may be authorized in quantities as follows:

1. Intravenous (IV) formulation:

a. Initial authorization – Belimumab may be covered in quantities up to 8 infusions in a 6 month period, based on a recommended initial dosing interval of every 2 weeks for 3 doses, followed by dosing every 4 weeks.

NOTE: Alternative Site of Care criteria will be waived for payment of the first dose, to allow for adequate transition time to arrange for a non-hospital outpatient setting for the infusion.

b. Continued authorization – A maximum of 6 infusions in a 24-week period, based on a recommended infusion interval of 4 weeks.

2. Subcutaneous (SC) formulation: Up to four of the 200 mg autoinjectors/ pre-filled syringes per 28 days for 24 weeks.

D. Authorization shall be reviewed at least every 24-weeks to confirm that current medical necessity criteria are met, and that the medication is effective when criterion 1, 2, or 3 below is met:

1. Patient's daily required dose of oral corticosteroids has decreased since the previous authorization.

OR

2. There is documented improvement in functional impairment.

OR

3. There has been a decrease in the number exacerbations since initiating belimumab.

III. Belimumab is considered investigational when used for all other conditions, including but not limited to:

A. Central nervous system (CNS) systemic lupus erythematosus.

B. Glomerulonephritis.

C. Idiopathic thrombocytopenic purpura (ITP).

D. Lupus nephritis.

E. Myasthenia gravis.

F. Pre-renal transplant desensitization.

G. Primary Sjögren's syndrome.

H. Rheumatoid arthritis.

I. Systemic lupus erythematosus in patients who are seronegative.

J. Vasculitis.

K. Waldenström's macroglobulinemia.

Position Statement [1-7]

Summary

- Belimumab is an intravenously infused monoclonal antibody that inhibits human B lymphocyte stimulator (BLyS) protein, and has only been studied for the treatment of active systemic lupus erythematosus (SLE).
- Belimumab was shown to be ineffective in seronegative patients, and is therefore only indicated in patients with active SLE who are auto-antibody positive (seropositive).
- The vast majority of subjects included in clinical trials with belimumab had SLE with musculoskeletal and/or mucocutaneous involvement. Additionally, significant improvement from baseline to study end was limited to these organ systems.
    * Patients with severe renal or severe CNS lupus were excluded from clinical trials of belimumab. There were not enough subjects with mild-to-moderate renal or CNS lupus to determine the benefit of belimumab in these organ systems. Renal and central nervous system (CNS) manifestations are associated with poor outcomes and mortality.
- All patients in phase 3 clinical trials with belimumab were receiving standard therapy. Current standard therapy includes various combinations of aspirin, NSAIDs, corticosteroids, antimalarial drugs (e.g. hydroxychloroquine) and/or immunosuppressive agents (e.g. cyclophosphamide, azathioprine, methotrexate, and mycophenolate mofetil), most of which are generically available.
- Belimumab has not been studied as first-line treatment or as monotherapy for SLE.
- Belimumab is administered as an intravenous (IV) infusion every 2 weeks for 3 doses, followed by dosing every 4 weeks, the dose and route shown to be safe and effective in clinical trials.
- New technologies and pharmaceuticals allow therapeutic services, such as infusion therapy, to be administered safely, effectively, and much less costly outside of higher-cost settings, such as the hospital outpatient setting. Alternative sites of care (such as doctor's offices, infusion centers, and home infusion) are well-established, accepted by physicians, and reduce the overall cost of care.

Clinical Efficacy

- The clinical benefit of belimumab, in addition to standard care, for reducing disease activity in patients with active, seropositive SLE is uncertain.
- Belimumab may be beneficial for a niche group of patients. The most promising results were shown in the organ systems associated with lower morbidity and mortality (mucocutaneous and musculoskeletal); however, only patients with active, seropositive SLE who were receiving other therapies were studied.
- The safety and efficacy of belimumab versus placebo have been evaluated in two unreliable phase 3, randomized controlled trials in 1,693 adult patients with active, auto-antibody positive SLE who were receiving standard therapy. [5,6]
    * Auto-antibody positive status was defined as an antinuclear antibody (ANA) titer ≥ 1:80 or an anti-double-stranded DNA concentration ≥ 30 IU/mL.
        - Higher ANA titers, such as 1:320, indicate positive disease. The second number

(i.e. 320) indicates the number of dilutions required for antinuclear antibodies to no longer be detected. The higher the second number, the higher the concentration of antibodies present.

* The studies were appraised as unreliable due to major flaws, which included but were not limited to:

    - The SLE Responder Index (SRI) is a non-validated measure that intends to capture clinically meaningful change in SLE disease activity. The definition of clinically meaningful improvement utilized as part of the SRI (≥ 4-point decrease in SELENA-SLEDAI) is not consistent with the American College of Rheumatology (ACR) definition of clinically meaningful improvement in SELENA-SLEDAI (≥ 7-point decrease). [7]
    - Both studies had a high proportion of patients that did not complete the studies (23.7% and 18.5%). [5,6]
- A phase 2 study evaluating the use of belimumab in patients with SLE demonstrated a lack of efficacy in patients who were auto-antibody negative. [9] Patients who have auto-antibody negative disease typically have a better prognosis.
- There are no studies to date evaluating the safety and effectiveness of belimumab relative to other medications for the treatment of SLE.

CNS Lupus [1]

- Patients with severe active CNS lupus were excluded from clinical trials of belimumab (Benlysta). Severe active CNS lupus was defined as seizures, psychosis, organic brain syndrome, cerebrovascular accident, cerebritis or CNS vasculitis requiring therapeutic intervention in the 60 days prior to initiation of belimumab.
- Patients with mild to moderate CNS lupus were included in the study; however < 3% of patients receiving belimumab in clinical trials had CNS involvement at baseline.
- Less than 50% of patients with baseline CNS involvement had improvement at week 52. Improvement in CNS involvement with belimumab was statistically significant relative to placebo in one pivotal trial, but not in the other. Studies including more patients with CNS involvement are needed to determine efficacy in this setting.

Lupus Nephritis [1]

- Patient with severe active lupus nephritis were excluded from clinical trials of belimumab. Severe active lupus nephritis was defined as having either proteinuria > 6 g/24 hours or serum creatinine > 2.5 mg/dL. Kidney biopsies are also utilized for the diagnosis of lupus nephritis.
- Approximately 15% of patients had SLE with renal involvement at baseline, as measured by the SELENA-SLEDAI scale.
- The American College of Rheumatology defines a renal disorder, as associated with SLE, to be persistent proteinuria > 0.5 g per day or > 3+, or as having cellular casts. Approximately 20% of patients included in clinical trials of belimumab had proteinuria > 0.5 g per day; however, it is unclear if these patients were considered to have lupus nephritis (mild or moderate).
- In clinical trials of belimumab, < 50% of patients with renal involvement at baseline showed improvement at week 52. The difference in improvement from baseline to week 52 was not statistically significant between belimumab and placebo.

- At week 52, approximately 6% of patients who had disease without renal involvement at baseline had newly developed renal involvement. The development of renal involvement was not statistically significant between belimumab and placebo.
- The ACR guidelines acknowledge the lack of evidence to support the use of belimumab in patients with lupus nephritis and do not list belimumab as a recommended therapy. [12]
- Trials in patients with lupus nephritis are ongoing. [10]

Safety

- In clinical trials, belimumab appeared to be associated with an increase in death, serious adverse events, infections and serious infections, as well as neurologic and psychiatric adverse events relative to placebo.
    * There were 14 deaths reported during the controlled period of the clinical trials with belimumab, and one death reported 15 weeks following treatment discontinuation. [1]
        - Six of the 15 deaths occurred in patients treated with belimumab 10 mg/kg (the FDA-approved treatment dose), six deaths occurred in the belimumab 1 mg/kg groups and three deaths occurred in the placebo groups.
        - Fifteen additional deaths have been reported in the open-label extension trials of belimumab 10 mg/kg in SLE and in trials for rheumatoid arthritis, with 14 occurring in patients treated with belimumab and one occurring with placebo.
        - Causes of death included infection, respiratory failure, malignancy, thrombocytopenia, suicide, cardiovascular events, SLE-related complications and unknown causes.
    * In April 2014 the belimumab prescribing information was updated to include a specific warning/precaution that cases of JC virus-associated progressive multifocal leukoencephalopathy (PML) have been reported in patient with SLE receiving immunosuppressants, including belimumab. [8]
        - Reported PML cases have resulted in neurological deficits, including fatal cases.
        - Patients receiving immunosuppressants, including belimumab, should be evaluated and monitored for deteriorating neurological signs and symptoms.
- The most commonly reported adverse reactions reported with belimumab 10 mg/kg (incidence of ≥ 3 % and at least 1% more frequently than placebo) include: *nausea, diarrhea, pyrexia, nasopharyngitis, bronchitis, insomnia, pain in extremity, depression, migraine, pharyngitis, cystitis, leucopenia, and viral gastroenteritis*. [8]
- The proportion of patients who discontinued treatment due to adverse events during clinical trials was 6.2% for patients receiving belimumab and 7.1% for patients receiving placebo. [1,4-6]
- There is currently no Risk Evaluation and Mitigation Strategy (REMS) Program is in place for belimumab; however, there is a medication guide for the use of belimumab.
- The use of belimumab in combination with intravenously administered cyclophosphamide has not been studied, and is therefore not recommended. [8]

Dosing Considerations

- Belimumab is dosed at 10 mg/kg every 2 weeks for the first three doses, and every four weeks thereafter. [8]
- Belimumab is administered via intravenous infusion over a 1 hour period by healthcare practitioners prepared to manage anaphylaxis. [8]
- Patients receiving treatment with intravenously administered cyclophosphamide or other biologics were excluded from clinical trials with belimumab. The safety and efficacy of belimumab when given concomitantly with intravenous cyclophosphamide or other biologics is unknown. [8]

Other Indications

- There are currently registered clinical trials evaluating belimumab for pre-renal transplant desensitization, primary Sjögren's syndrome, Waldenström's macroglobulinemia, rheumatoid arthritis, systemic sclerosis, myasthenia gravis, myositis, and vasculitis, such as Wegener's granulomatosis and microscopic polyangiitis. [10]
- A published phase 2 trial compared the efficacy of several doses of belimumab to placebo for treating patients with rheumatoid arthritis who were previously treated with at least one disease-modifying anti-rheumatic drug (DMARD). The statistical significance of improvements with belimumab vs placebo was inconsistent across doses. Additional well-designed trials are needed to establish the efficacy and safety of belimumab in rheumatoid arthritis. [11]
- There are no published randomized controlled trials demonstrating efficacy of belimumab in other conditions.

Cross References
Site of Care Review, Medication Policy Manual, Policy dru408

Codes	**Number**	**Description**
HCPCS	J0490	Injection, belimumab, 10 mg

References

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Revision History

Revision Date	Revision Summary
8/14/2017	Added SC formulation to policy.
4/14/2017	No changes to coverage criteria with this annual update.
4/8/2016	No changes