Lupus Prior Authorization with Quantity Limit Program Summary

Your health benefit plan may not cover certain prescription drug products or drug categories included in this document. Please consult your benefit plan materials for details about your particular benefit.

This document may include drugs that are not included on your plan's formulary. For drug coverage status, please consult your plan's formulary.

FDA APPROVED INDICATIONS AND DOSAGE[1,9]

Agent(s)	Indication(s)	Dosage
Benlysta® (belimumab) Subcutaneous solution Injection powder	Treatment of patients 5 years and older with active, autoantibody positive, systemic lupus erythematosus who are receiving standard therapy Limitation of use: efficacy has not been evaluated in patients with severe active central nervous system lupus. It has not been studied in combination with other biologics so is not recommended in these situations.	**IV (adults and pediatrics)**: 10 mg/kg at 2-week intervals for the first 3 doses, then at 4-week intervals thereafter **SC (adults only)**: 200 mg once weekly (must be 18 years and older)
	Treatment of adult patients with active lupus nephritis who are receiving standard therapy	**IV:** 10 mg/kg at 2-week intervals for the first 3 doses, then at 4-week intervals thereafter **SC**: 400 mg once weekly for 4 doses, then 200 mg once weekly thereafter
Lupkynis™ (voclosporin) Capsule	In combination with a background immunosuppressive therapy regimen for the treatment of adult patients with active lupus nephritis Limitation of use: safety and efficacy of Lupkynis have not been established in combination with cyclophosphamide. Use is not recommended in this situation.	23.7 mg orally twice daily

CLINICAL RATIONALE
Systemic Lupus Erythematosus (SLE)

Systemic Lupus Erythematosus (SLE) is a chronic inflammatory autoimmune disease of unknown cause. It has a broad range of clinical and serological manifestations and can affect many organs. Clinical symptoms of SLE include fatigue, fever, arthralgia, myalgia, changes in weight, skin and mucus membrane lesions and ulcers, and vascular disease. SLE can also include cardiac, renal, pulmonary, and neurologic involvement. Due to its multisystem involvement and likelihood of changes in presentation, the diagnosis of SLE may be difficult.[2]

The American College of Rheumatology (ACR) recommend referral to a rheumatologist and/or another appropriate specialist to establish the diagnosis of SLE; assess activity and severity level; and management of the disease.[3]

The 2019 update of the EULAR recommendations for the management of SLE recommend the following[5]:

- Hydroxychloroquine is recommended for all patients with SLE, unless contraindicated, at a max dose of 5 mg/kg/real body weight (BW)
- Glucocorticoids may be used for rapid symptoms relief, but long-term goals should be to minimize daily glucocorticoid dose to ≤7.5 mg/day prednisone equivalent or discontinue
- Immunosuppressive therapies should be initiated in patients that are not responding to hydroxychloroquine (alone or in combination with glucocorticoids) OR in patients that are unable to reduce the glucocorticoid dose to the recommended maintenance dose
- Immunosuppressive therapies include methotrexate, azathioprine, or mycophenolate
- Cyclophosphamide can be used for severe organ or life threatening SLE as well as rescue therapy for those patients that do not respond to other immunosuppressive agents
- Add on treatment with belimumab should be considered in patients with inadequate response to standard of care therapy (combinations of hydroxychloroquine and glucocorticoids with or without immunosuppressive agents), defined as residual disease activity not allowing tapering of glucocorticoids and/or frequent relapses
- Rituximab may be considered in organ-threatening refractory disease or in those with intolerance/contraindication to standard immunosuppressive agents

HHS notes that the same management strategies apply to children and adolescents with SLE.[4]

Lupus Nephritis

Lupus nephritis (LN) is a common cause of kidney injury and failure in patients with SLE. Roughly 50% of patients with SLE will develop LN at some point in their SLE disease course and between 10% to 30% of those patients will progress to kidney failure requiring kidney transplant. Mortality in patients with LN is significantly higher than those that do not develop LN, with death occurring in 5% to 25% of patients with proliferative LN. LN typically develops early in SLE disease course and can often be present at initial diagnosis of SLE. LN results due to an accumulation of immune complex in the glomeruli. Intrarenal inflammation occurs leading to permanent damage to the kidney.[6]

Diagnosis of LN can be challenging, especially if the patient has not been initially diagnosed with SLE. Serum creatinine levels, urine dipstick testing, and urine sediment are necessary tools for LN evaluation. Proteinuria in patients with SLE is suggestive of a diagnosis of LN.[6] The American College of Rheumatology (ACR) indicates that all patients with clinical evidence of LN should undergo a renal biopsy to determine disease classification and confirm diagnosis of LN. The ACR also indicates that treatment should be based off of the International Society of Nephrology/Renal Pathology Society (ISN/RPS) LN classification. The ISN/RPS breaks down LN into the following 6 classes[8]:

- Class I: minimal mesangial lupus nephritis
- Class II: mesangial proliferative lupus nephritis
- Class III: focal lupus nephritis
- Class IV: diffuse lupus nephritis
- Class V: membranous lupus nephritis

- Class VI: advanced sclerotic lupus nephritis

The ACR recommends the following for the treatment of lupus nephritis[7]:
- Class I and II: do not usually require immunosuppressive treatment
- Class III and IV, Class V when combined with class III or IV: require aggressive therapy with glucocorticoids and immunosuppressive agents
- Class V alone or Class VI: prepare for kidney transplant
- Induction therapy for class III, IV, and V when combined with class III or IV should consist of mycophenolate mofetil (MMF) or IV cyclophosphamide plus glucocorticoids for 6 months
- Improvement after 6 months of induction therapy: recommendation is to switch patients to MMF or azathioprine (AZA) with or without glucocorticoids for maintenance therapy
- No improvement after 6 months of induction therapy:
    - Switch the patient to the other induction agent in combination with glucocorticoids for another 6 months
    - If improvement is seen after 6 months, switch to maintenance therapy noted above
    - If no improvement after 6 months, switch to rituximab or calcineurin inhibitors in combination with glucocorticoids

Safety[1]
Benlysta is contraindicated in patients that have experienced anaphylaxis with belimumab.

Lupkynis is contraindicated in the following:
- Patients concomitantly using strong CYP3A4 inhibitors ((e.g., ketoconazole, itraconazole, clarithromycin) because these medications can significantly increase exposure to Lupkynis which may increase the risk of acute and/or chronic nephrotoxicity
- Patients who have a known serious or severe hypersensitivity reaction to Lupkynis or any of its excipients

Efficacy[1]
Benlysta SLE Clinical Trials
The safety and efficacy of belimumab was evaluated in two randomized, double-blind, placebo-controlled, phase III studies involving patients age 18 and older with SLE (BLISS-52 and BLISS-76 study). The design of these studies was based on the results of a phase II study which identified that patients who were autoantibody-positive had a better response to belimumab. As a result, BLISS-52 and BLISS-76 limited the study population to only include autoantibody-positive SLE patients. Patients were on a standard of care SLE treatment regimen comprising of at least one of the following: corticosteroids, antimalarials, nonsteroidal anti-inflammatory drugs (NSAIDS), and/or immunosuppressives (azathioprine, methotrexate, or mycophenolate). Patients with severe active lupus nephritis and severe central nervous system (CNS) lupus were excluded. Patients using other biologics including B-cell targeted therapies such as rituximab or intravenous cyclophosphamide in the previous six months were also excluded.

BLISS-52 (N=865) and BLISS-76 (N=826) had similar designs with the exception of duration. BLISS-76 was 76 weeks in duration and BLISS-52 was 52 weeks in length. Eligible patients had active SLE disease which was defined as a Safety of Estrogen in Lupus Erythematosus National Assessment-SLE Disease Activity Index (SELENA-SLEDAI) score $\geq$6. Patients were randomly assigned to receive belimumab 1 mg/kg, 10 mg/kg, or placebo in addition to standard of care. The study medication was administered on Days 0, 14, 28, and then every 28 days for 48 weeks in BLISS-52 and 72 weeks in BLISS-76.

In both BLISS-52 and BLISS-76, the proportion of SLE patients achieving a SLE Responder Index-4 (SRI-4) response was significantly higher in the belimumab 10 mg/kg group than placebo while the effect on SRI-4 was not consistently significantly different for the belimumab 1 mg/kg group.

The safety and efficacy of Benlysta in pediatric patients was evaluated in an international, randomized, double-blind, placebo-controlled, 52-week study conducted in 93 patients with a clinical diagnosis of SLE according to the ACR classification criteria. Patients had a SELENA-SLEDAI score $\geq$6 and positive autoantibodies at screening. Patients were on stable SLE treatment regimen and had similar inclusion and exclusion criteria as in the adult studies. The primary endpoint was the same as the adult trials, and there was a numerically higher proportion of pediatric patients achieving a response in SRI-4 and its components in patients receiving Benlysta plus standard therapy compared with placebo plus standard therapy (53% vs 44%, odds ratio 1.49 [CI 0.64, 3.46]).

Benlysta LN Clinical Trials
The safety and efficacy of Benlysta in patients with lupus nephritis was evaluated in a 104 week, randomized, double-blind, placebo controlled trial that included 448 patients with active proliferative and/or membranous lupus nephritis. Patients had to be at least 18 years of age and ANA positive SLE that fulfilled the ACR classification criteria. Patients were required to have a urine protein to creatinine ratio of 1 or more and biopsy-proven lupus nephritis ISN/RPS class III, IV, or V. Induction therapy had to be initiated within 60 days before randomization and therapies had to include either induction with glucocorticoids in combination with MMF or IV cyclophosphamide, followed by MMF or AZA for maintenance therapy.

The primary efficacy endpoint was Primary Efficacy Renal Response (PERR) at week 104, defined as a response at Week 100 confirmed by a repeat measurement at week 104 of the following parameters: urine protein:creatinine ratio (uPCR) ≤0.7 g/g and estimated glomerular filtration rate (eGFR) ≥60 mL/min/1.73 m2 or no decrease in eGFR of >20% from pre-flare value.

The major secondary endpoints included Complete Renal Response (CRR) (defined as a response at week 100 confirmed by a repeat measurement at week 104 of the following parameters: uPCR <0.5 g/g and eGFR ≥90 mL/min/1.73 m2 or no decrease in eGFR of >10% from pre-flare value); PERR at week 52; and time to renal-related event or death (renal-related event defined as first event of end-stage renal disease, doubling of serum creatinine, renal worsening [defined by quantified increase in proteinuria and/or impaired renal function], or receipt of renal disease-related prohibited therapy due to inadequate lupus nephritis control or renal flare management).

The proportion of patients achieving PERR at Week 104 was significantly higher in patients receiving Benlysta plus standard therapy compared with placebo plus standard therapy (43% vs 32%, p=0.031). The subgroup analysis of PERR and CRR by biopsy class indicated the odds ratios for patients with class 5 without combined class III or class IV favored placebo plus standard therapy over Benlysta plus standard therapy. The odds ratio for all other classes or combinations favored Benlysta plus standard therapy. Most of the secondary endpoint were statistically significant (CRR at week 100 p=0.017 [30% vs 20% Benlysta vs placebo], PERR at week 52 p=0.025 [47% vs 35% Benlysta vs placebo]). The table below shows the time to renal related event or death.

End point	Placebo + standard therapy (n=223) No. (%)	Benlysta + standard therapy (n=223) No. (%)
Any Event	63 (28%)	35 (16%)

Death from any cause	2	1
Progression to ESRD	1	0
Doubling of creatinine level from baseline	1	1
Increased proteinuria, impaired kidney function, or both	39	17
Treatment failure related to kidney event	20	16

Lupkynis LN trial
The safety and efficacy of Lupkynis were investigated in a 52-week, randomized, double-blind, placebo-controlled trial in patients with a diagnosis of systemic lupus erythematosus and with International Society of Nephrology/Renal Pathology Society (ISN/RPS) biopsy-proven active Class III or IV LN (alone or in combination with Class V LN) or Class V LN. A total of 357 patients with LN were randomized in a 1:1 ratio to receive either Lupkynis 23.7 mg twice daily or placebo. Patients in both arms received background treatment with MMF and corticosteroids.

The primary efficacy endpoint was the proportion of patients achieving complete renal response at week 52. In order to be considered a responder, the patient must not have received more than 10 mg prednisone for ≥3 consecutive days or for ≥7 days in total during weeks 44 through 52. Patients who received rescue medication or withdrew from the study were considered non-responders. A higher proportion of patients in the Lupkynis arm than the placebo arm achieved complete renal response at week 52 (Lupkynis 40.8% vs placebo 22.5%, p<0.001).

A higher proportion of patients in the Lupkynis arm than the placebo arm achieved complete renal response at week 24 (32.4% vs. 19.7%; odds ratio: 2.2; 95% CI: 1.3, 3.7). Time to UPCR of ≤0.5 mg/mg was shorter in the Lupkynis arm than the placebo arm (median time of 169 days vs. 372 days; hazard ratio: 2.0; 95% CI: 1.5, 2.7).

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Lupus Prior Authorization with Quantity Limit

TARGET AGENT(S)
Benlysta® (belimumab)
Lupkynis™ (voclosporin)

Brand (generic)	GPI	Multisource Code	Quantity Limit (per day or as listed)
Benlysta (belimumab)			
120 mg vial	99422015002120	M, N, O, or Y	N/A
400 mg vial	99422015002140	M, N, O, or Y	N/A
200 mg/mL autoinjector	9942201500D520	M, N, O, or Y	4 syringes/28 days
200 mg/mL prefilled syringe	9942201500E520	M, N, O, or Y	4 syringes/28 days
Lupkynis (voclosporin)			
7.9 mg capsule	99402080000120	M, N, O, or Y	6 capsules

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL
Initial Evaluation
Target Agent(s) will be approved when ALL of the following are met:

1. ONE of the following:
    A. The requested agent is eligible for continuation of therapy AND ONE of the following:
        i. Information has been provided that indicates the patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days
        OR
        ii. The prescriber states the patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days AND is at risk if therapy is changed

Agents Eligible for Continuation of Therapy
All target agents are eligible

    OR
    B. The patient has a diagnosis of active systemic lupus erythematosus (SLE) disease WITHOUT active Lupus Nephritis **AND** ALL of the following:
        i. The requested agent is FDA approved for SLE
        AND
        ii. BOTH of the following:
            a. ONE of the following:
                1. The patient has tried and had an inadequate response to hydroxychloroquine
                OR
                2. The patient has an intolerance or hypersensitivity to hydroxychloroquine
                OR
                3. The patient has an FDA labeled contraindication to hydroxychloroquine
            AND
            b. ONE of the following:
                1. The patient has tried and had an inadequate response to corticosteroids OR immunosuppressives (i.e., azathioprine, methotrexate, oral cyclophosphamide, mycophenolate)
                OR

2. The patient has an intolerance or hypersensitivity to therapy with corticosteroids OR immunosuppressives (i.e., azathioprine, methotrexate, oral cyclophosphamide, mycophenolate)
OR
3. The patient has an FDA labeled contraindication to ALL corticosteroids AND immunosuppressives (i.e., azathioprine, methotrexate, oral cyclophosphamide, mycophenolate)

AND

iii. ONE of the following:
a. The patient is 18 years of age and over
OR
b. The patient is 5 to 17 years of age AND the request is for IV administration

OR

C. The patient has a diagnosis of active lupus nephritis AND ALL of the following:
i. The requested agent is FDA approved for lupus nephritis
AND
ii. The patient has Class III, IV, or V lupus nephritis confirmed via kidney biopsy
AND
iii. ONE of the following:
a. The patient's age is within FDA labeling for the requested indication for the requested agent
OR
b. The prescriber has provided information in support of using the requested agent for the patient's age

OR

D. BOTH of the following:
i. The patient has another FDA approved indication for the requested agent
AND
ii. ONE of the following:
a. The patient's age is within FDA labeling for the requested indication for the requested agent
OR
b. The prescriber has provided information in support of using the requested agent for the patient's age

AND

2. ONE of the following:
A. The patient has a diagnosis of active systemic lupus erythematosus (SLE) disease WITHOUT active Lupus Nephritis AND BOTH of the following:
i. The patient is currently treated with standard SLE therapy (i.e., corticosteroids, hydroxychloroquine, azathioprine, methotrexate, oral cyclophosphamide, mycophenolate)
AND
ii. The patient will continue standard SLE therapy (i.e., corticosteroids, hydroxychloroquine, azathioprine, methotrexate, oral cyclophosphamide, mycophenolate) in combination with the requested agent

OR

B. The patient has a diagnosis of active lupus nephritis AND BOTH of the following:
i. The patient is currently treated with standard lupus nephritis therapy (i.e., azathioprine, mycophenolate, IV cyclophosphamide may also be accepted for Benlysta)
AND

ii. The patient will continue standard lupus nephritis therapy (i.e., azathioprine, mycophenolate, IV cyclophosphamide may also be accepted for Benlysta) in combination with the requested agent

OR

C. The patient has another FDA approved indication for the requested agent

AND

3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., rheumatologist, nephrologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis

AND

4. The patient does NOT have severe active central nervous system lupus

AND

5. If the requested agent is Benlysta, the patient will NOT be using the requested agent in combination with another biologic agent

AND

6. If the requested agent is Lupkynis, the patient will NOT be using the requested agent in combination with cyclophosphamide

AND

7. The patient does NOT have any FDA labeled contraindications to the requested agent

AND

8. ONE of the following:
   A. The requested agent does not have a program quantity limit AND the requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication

   OR

   B. The requested quantity (dose) does NOT exceed the program quantity limit

   OR

   C. ALL of the following:
      i. The requested quantity (dose) is greater than the program quantity limit

      AND

      ii. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication

      AND

      iii. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the program quantity limit

Length of Approval: 12 months

*NOTE: Approve Benlysta subcutaneous loading dose for 1 month, then maintenance dose can be approved for the remainder of 12 months

Renewal Evaluation

Target Agent(s) will be approved when ALL of the following are met:

1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process

AND

2. ONE of the following:
   A. The patient has a diagnosis of active systemic lupus erythematosus (SLE) disease WITHOUT active Lupus Nephritis AND ALL of the following:
      i. The requested agent is FDA approved for SLE

      AND

      ii. The patient will continue standard SLE therapy (i.e., corticosteroids, hydroxychloroquine, azathioprine, methotrexate, oral cyclophosphamide, mycophenolate)

AND

iii. The patient has had clinical benefit with the requested agent

AND

iv. ONE of the following:

a. The patient is 18 years of age and over

OR

b. The patient is 5 to 17 years of age AND the request is for IV administration

OR

B. The patient has a diagnosis of active lupus nephritis AND ALL of the following:

i. The requested agent is FDA approved for lupus nephritis

AND

ii. The patient will continue standard lupus nephritis therapy (i.e., azathioprine, mycophenolate)

AND

iii. The patient has had clinical benefit with the requested agent

OR

C. The patient has another FDA approved indication for the requested agent AND has had clinical benefit with the requested agent

AND

3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., rheumatologist, nephrologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis

AND

4. The patient does NOT have severe active central nervous system lupus

AND

5. If the requested agent is Benlysta, the patient will NOT be using the requested agent in combination with another biologic agent

AND

6. If the requested agent is Lupkynis, the patient will NOT be using the requested agent in combination with cyclophosphamide

AND

7. The patient does NOT have any FDA labeled contraindications to the requested agent

AND

8. ONE of the following:

A. The requested agent does not have a program quantity limit AND the requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication

OR

B. The requested quantity (dose) does NOT exceed the program quantity limit

OR

C. ALL of the following:

i. The requested quantity (dose) is greater than the program quantity limit

AND

ii. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication

AND

iii. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the program quantity limit

a.

Length of Approval: 12 months

