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Prior Authorization Criteria Update: Belimumab

Purpose of Update:

- To review new evidence for the safety and efficacy of belimumab for treatment of adults with active lupus nephritis who are receiving standard therapy.

The FDA approved an expanded indication for the use of belimumab in adults with active lupus nephritis March 2021.[1] Belimumab was initially approved for treatment of patients aged 5 years and older with active, autoantibody-positive systemic lupus erythematosus (SLE).[1] Patients with acute, severe lupus nephritis were excluded from the initial phase 3 clinical trials which led to FDA approval of belimumab. Lupus nephritis, which occurs in 25 to 60% of patients with SLE, is the most common severe manifestation of SLE and a major cause of illness and death.[2]

The expanded indication for lupus nephritis was based on a phase 3, multinational, multicenter, randomized double-blind placebo-controlled trial.[3] A total of 448 patients were enrolled in the trial and randomized 1:1 to belimumab or placebo. Belimumab was dosed at 10 mg per kg, administered intravenously on Days 0, 14, 28, and then every 28 days in addition to standard therapy. Standard therapy included: corticosteroids with 1) oral mycophenolate mofetil (MMF) for induction followed by MMF for maintenance, or 2) intravenous cyclophosphamide for induction followed by oral azathioprine for maintenance.[3] Patients were required to be at least 18 years old, with autoantibody-positive SLE and biopsy-proven, active lupus nephritis. International Society of Nephrology and Renal Pathology Society (ISN/RPS) lupus nephritis classifications are presented in **Table 1**. At screening, the patients had a ratio of urinary protein to creatinine of 1 or more and ISN/RPS biopsy-proven class III, IV, or V lupus nephritis within 6 months before, or during, screening.[3] Patients who had been on dialysis within the last year or with severe renal impairment (estimated glomerular filtration rate [eGFR] less than 30 ml/minute/1.73 m^2) were excluded from randomization.[3]

Table 1. ISN/RPS Lupus Nephritis Classifications[4]

Status	Description
Class I	Minimal mesangial lupus nephritis: earliest and mildest form of glomerular involvement
Class II	Mesangial proliferative lupus nephritis: excellent prognosis and no specific therapy is indicated
Class III	Focal lupus nephritis: patients present with hematuria and proteinuria, possibly to also have hypertension, decreased renal function and/or nephrotic syndrome. Light microscopy reveals less than 50 percent of glomeruli are affected.
Class IV	Diffuse lupus nephritis: patients present with hematuria and proteinuria and frequently seen with hypertension, decreased renal function and nephrotic syndrome. Light microscopy reveals more than 50 percent of glomeruli are affected.
Class V	Lupus membranous nephropathy: patients present with signs of nephrotic syndrome
Class VI	Advanced sclerosing lupus nephritis: patients present with slowly progressive kidney dysfunction associated with proteinuria

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The trial was conducted at 107 sites located in Asia (47% of trial sites), North America (17%), South America (16%), and Europe (19%).[3] Mean patient age was 33 years (range: 18 to 77); the majority (88%) were female and Asian (50%).[3] Over half of the patients (58%) has Class III or IV lupus nephritis.[3] GlaxoSmithKline contributed to the design, data collection, and data analysis of the trial.

The primary endpoint was a composite assessment of primary efficacy renal response (PERR) at week 104, defined as a ratio of urinary protein to creatinine less than or equal to 0.7, an eGFR no worse than 20% below pre-flare value or greater than or equal to 60 ml/minute/1.73m^2 of body surface area (BSA), and no use of glucocorticoid rescue therapy for treatment failure.[3] Secondary endpoints included complete renal response (CRR) at week 104 (a ratio of urinary protein to creatinine of less than 0.5, an eGFR that was no worse than 10% below the pre-flare value or greater than or equal to 90 ml/minute/1.73 m^2 BSA, and no use of rescue therapy), PERR at week 52, and the time to a renal-related event or death.[3] At week 104, 43% (n=96) of the belimumab group versus 32% (n=72) of the placebo group had a PERR response (odds ratio [OR] 1.6, 95% confidence interval [CI] 1.0 to 2.3, p=0.03).[3] At week 104, more patients who received belimumab had a CRR compared to those who received placebo (30% vs. 20%, respectively; OR 1.7, 95% CI 1.1 to 2.7, p=0.02).[3] At week 52, 47% (n=104) of the belimumab group and 20% (n=79) of the placebo group had a PERR (OR 1.6, 95% CI 1.1 to 2.4, p=0.02).[3] The group of patients who received belimumab had a significantly lower risk of a renal-related event or death during the trial than the group of patients who received placebo (hazard ratio, 0.51; 95% CI, 0.34 to 0.77; P=0.001).[3] These results were primarily because of increased proteinuria, impaired kidney function, or both (in 17 patients in the belimumab group and 39 patients in the placebo group) or kidney-related treatment failure (in 16 and 20 patients, respectively).[3] One death from any cause was observed in the belimumab group compared with 2 in the placebo group.[3] There were no new safety events identified in this trial compared to previous trials of belimumab.[3]

Black patients with lupus nephritis are more likely to have a worse prognosis than those in other racial groups.[3] This study enrolled a low proportion of Black patients (14%), which limits applicability of study results to Black patients. Black patients who received belimumab appeared to be more likely to have a PERR and a CRR at week 104 than those who received placebo.[3] However, in both groups, the percentage of Black patients who had a response was lower than the percentage of patients in the overall population who had a response.[3] Other trial limitations were the low percentage of patients receiving cyclophosphamide–azathioprine (27%) compared with mycophenolate (73%).[3] Only two induction and maintenance regimens were permitted as background therapy, although additional therapies for lupus nephritis, such as calcineurin inhibitors, are currently used in practice.[3] In addition, patient-reported outcomes were not included.[3]

Recommendation:

- Update the prior authorization criteria for belimumab to include the expanded FDA indication for treatment of adults with active lupus nephritis.

References:

1. Belimumab (BENLYSTA) Package Insert. Philidelphia, PA: GlaxoSmithKline, March 2021.
2. Hanly JG, O'Keeffe AG, Su L, et al. The frequency and outcome of lupus nephritis: results from an international inception cohort study. *Rheumatology (Oxford)*. Feb 2016;55(2):252-62. doi:10.1093/rheumatology/kev311.
3. Furie R, Rovin BH, Houssiau F, et al. Two-Year, Randomized, Controlled Trial of Belimumab in Lupus Nephritis. *New England Journal of Medicine*. 2020;383(12):1117-1128..
4. Bajema IM, Wilhelmus S, Alpers CE, et al. Revision of the International Society of Nephrology/Renal Pathology Society classification for lupus nephritis: clarification of definitions, and modified National Institutes of Health activity and chronicity indices. *Kidney Int.* 2018;93(4):789-796.

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Appendix 1. Prior Authorization Criteria

Belimumab (Benlysta®)

Goal(s):

- Promote use that is consistent with national clinical practice guidelines and medical evidence.

Length of Authorization:

- 6 months

Requires PA:

- Benlysta® (belimumab) pharmacy or physician administered claims.

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD-10 code.	
2. Is the diagnosis funded by OHP?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by the OHP.
3. Does the patient have severe active central nervous system lupus?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #4
4. Is this a request for continuation of therapy?	**Yes**: Go to **Renewal Criteria**	**No:** Go to #5
5. Is the patient diagnosed with lupus nephritis or systemic lupus erythematosus (SLE)?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness

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Approval Criteria		
6. Is belimumab dosed appropriately and with an approved formulation for patient's age as outlined in Table 1?	**Yes:** Go to # 7	**No:** Pass to RPh. Deny; medical appropriateness
7. Is the patient currently on other biologic therapy or intravenous cyclophosphamide?	**Yes:** Pass to RPh. Deny; medical appropriateness. Belimumab has not been studied in combination with other biologics or intravenous cyclophosphamide.	**No:** Go to # 8
8. Is the drug being prescribed by or in consultation with a rheumatologist, nephrologist, or a provider with experience treating SLE or lupus nephritis?	**Yes:** Go to # 9	**No:** Pass to RPh. Deny; medical appropriateness
9. Does the patient have active autoantibody-positive SLE or lupus nephritis and is a baseline assessment of SLE disease activity available using one of the following functional assessment tools: • SLE Index Score (SIS) • British Isles Lupus Assessment Group (BILAG) • Systemic Lupus Activity Measure (SLAM) • Systemic Lupus Erythematosus Disease Activity Score (SLEDAI) • Physicians Global Assessment (PGA) • Systemic Lupus International Collaborating Clinic (SLICC) Damage Index • Urinary protein to creatinine ratio • Most recent estimated Glomerular Filtration Rate (eGFR)	**Yes:** Go to # 10. Document baseline assessment _____.	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
10. Is the patient currently receiving standard of care treatment for Systemic Lupus Erythematosus (SLE) or lupus nephritis e.g., hydroxychloroquine, systemic corticosteroids, non-steroidal anti-inflammatory drugs, azathioprine, mycophenolate, or methotrexate?	**Yes:** Approve for 6 months.	**No:** Pass to RPh. Deny; medical appropriateness. Belimumab has not been studied as monotherapy in patients with SLE.

Renewal Criteria		
1. Is the patient currently on other biologic therapy or intravenous cyclophosphamide?	**Yes:** Pass to RPh. Deny; medical appropriateness. Belimumab has not been studied in combination with other biologics or intravenous cyclophosphamide.	**No:** Go to #2
2. Has the patient's SLE disease activity improved or stabilized as assessed by one of the following functional assessment tools: • SLE Index Score (SIS) • British Isles Lupus Assessment Group (BILAG) • Systemic Lupus Activity Measure (SLAM) • Systemic Lupus Erythematous Disease Activity Score (SLEDAI) • Physicians Global Assessment (PGA) • Systemic Lupus International Collaborating Clinic (SLICC) Damage Index • Urinary protein to creatinine ratio • eGFR	**Yes:** Approve for 6 months.	**No:** Pass to RPh; Deny; medical appropriateness.

Table 1: FDA approved ages

Indication	Approved formulation	
	Intravenous (IV) powder for solution	**Subcutaneous (SC) Injection**
Systemic Lupus Erythematosus (SLE)	5 years and older	18 years and older
Lupus Nephritis	18 years and older	18 years and older
IV (usual dosage): 10 mg/kg IV infusion over 1 hour every 2 weeks for the first 3 doses, then every 4 weeks thereafter **SC** (usual dosage): **SLE**: 200 mg SC once weekly **Lupus Nephriti**s:400 mg (two 200-mg injections) SC once weekly into abdomen or thigh for 4 doses, then 200 mg SC once weekly thereafter		

P&T/DUR Review: *8/21 (DM) 2/20 DM, 5/18 (DM)*
Implementation: *3/1/2020; 7/1/18*