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CADTH Reimbursement Recommendation

Belimumab (Benlysta)

Indication: In addition to standard therapy for treatment of active lupus nephritis in adult patients

Sponsor: GlaxoSmithKline Inc.

Final recommendation: Reimburse with conditions

CADTH

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Summary

CADTH

What Is the CADTH Reimbursement Recommendation for Benlysta?

CADTH recommends that Benlysta be reimbursed by public drug plans in addition to standard therapy for treatment of active lupus nephritis (LN) in adult patients.

Which Patients Are Eligible for Coverage?

Benlysta should only be covered to treat adult patients with class III or IV, with or without class V, or pure class V active LN and who have started standard induction therapy within the previous 60 days. Benlysta should not be covered to treat patients who previously failed induction therapies or patients with an estimated glomerular filtration rate less than 30 mL/min/1.73 m^2.

What Are the Conditions for Reimbursement?

Benlysta should only be reimbursed if prescribed by either a rheumatologist or nephrologist with experience managing LN and if the cost of Benlysta is reduced.

Why Did CADTH Make This Recommendation?

- Evidence from a clinical trial demonstrated that patients with class III or IV, with or without class V, or pure class V active LN treated with Benlysta experienced preservation or improvement in kidney function and reduced the levels of protein in the urine.
- Benlysta may address some of the needs that are important to patients because it improves renal response.
- Based on CADTH's assessment of the health economic evidence, Benlysta does not represent good value to the health care system at the public list price. A price reduction is therefore required.
- Based on public list prices, Benlysta is estimated to cost the public drug plans approximately $14 million over the next 3 years.

Additional Information

What Is Lupus Nephritis?

Systemic lupus erythematosus (SLE) is a disorder in which the body's immune system attacks its own cells and organs that occurs in about 1 in 2,000 individuals in Canada. LN is a complication of SLE that leads to kidney inflammation and may lead to protein and/or blood in the urine and impaired kidney function. This can worsen over time and lead to end-stage renal disease requiring dialysis or a kidney transplant. It is estimated that LN occurs in about 50% of patients with SLE.

Unmet Needs in Lupus Nephritis

Standard-of-care therapy is the only treatment available to patients with class III or IV, with or without class V, or pure class V active LN. Effective therapies with tolerable side effects that can reduce disease symptoms and disease progression are needed.

How Much Does Benlysta Cost?

Treatment with Benlysta is expected to cost approximately $20,631 to $25,938 per patient per year.

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that belimumab be reimbursed in addition to standard therapy for treatment of active lupus nephritis (LN) in adult patients only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One randomized, double-blind, placebo-controlled, phase III trial (BLISS-LN; N = 448) demonstrated that treatment with IV belimumab at a dose of 10 mg/kg resulted in added clinical benefit for patients with active LN. In the BLISS-LN trial, 104 weeks of treatment with belimumab was associated with statistically significant improvement in renal response compared with placebo as measured by the primary efficacy renal response (PERR). Statistically significant improvement was achieved by 96 (43.0%) patients in the belimumab treatment group and 72 (32.3%) patients in the placebo group, with an adjusted between–treatment group difference of 10.66% (95% confidence interval [CI],1.89 to 19.42; P = 0.0311). In addition, statistically significant differences in favour of the belimumab group were reported for all key secondary end points, including complete renal response (CRR) at week 104 (adjusted between-group difference = 10.27%; 95% CI, 2.40 to 18.14; P = 0.0167), PERR at week 52 (adjusted between–treatment group difference = 11.12%; 95% CI, 2.25 to 19.99; P = 0.0245), ordinal renal response (ORR) at week 104 (adjusted between-group difference = 10.27%; 95% CI, 2.40 to 18.14; P = 0.0167), and time to renal-related event or death (hazard ratio [HR] = 0.51; 95% CI, 0.34 to 0.77; P = 0.0014). The clinical expert stated that the benefits of belimumab reported in the BLISS-LN trial were clinically meaningful. Although other end points favoured belimumab, such as reduction in oral prednisone use, reduction in severe flares, and decreased disease activity as measured by the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-S2K) with modified scoring for proteinuria, these outcomes were considered supportive and were not adjusted for multiple statistical testing.

Patients and the clinical expert identified a need for treatment options that are effective in optimizing kidney function (i.e., preservation or improvement in estimated glomerular filtration rate [eGFR]) accompanied by reduction in proteinuria, reduction in fatigue and flares, reduction of oral prednisone use, and improved health-related quality of life (HRQoL). CDEC concluded that, based on the evidence, belimumab appears to address the most important unmet need identified by the patients by achieving improvement in renal response; however, no conclusions could be made regarding the effects of belimumab on the improvement of HRQoL.

Using the sponsor-submitted price for belimumab and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for belimumab plus mycophenolate mofetil (MMF) was $352,880 per quality-adjusted life-year (QALY) compared with MMF alone. At this ICER, belimumab plus MMF is not cost-effective at a willingness-to-pay threshold of $50,000 per QALY for adult patients with active LN. A price reduction is required for belimumab to be considered cost-effective at a $50,000 per QALY threshold.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Adult patients with active LN who are diagnosed with any of the following: 1.1. class III with or without class V 1.2. class IV with or without class V 1.3. class V (i.e., pure class V).	The BLISS-LN trial enrolled adult patients (age ≥ 18 years) with biopsy-proven active LN class III or IV, with or without class V, or pure class V membranous.	CDEC noted that patients must have biopsy-proven LN of International Society of Nephrology and Renal Pathology Society class III (focal LN) or IV (diffuse LN), with or without coexisting class V (membranous LN), or pure class V LN within 6 months of initiating treatment with belimumab.
2. Patients must have started standard induction therapy within the previous 60 days.	In the BLISS-LN trial, induction therapy was initiated within 60 days before randomization. In addition, 57.6% of patients initiated belimumab within 2 weeks of initiating induction therapy and 82.5% of patients initiated belimumab within 4 weeks of initiating induction therapy, which supports early initiation of treatment with belimumab after initiation of induction therapy.	Standard induction therapy is defined as corticosteroids with either cyclophosphamide or mycophenolate mofetil or other forms of mycophenolate. Outside of induction therapy, patients are expected to be receiving other standard-of-care therapies for LN (e.g., antimalarials and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers) as indicated.
3. Treatment with belimumab must not be reimbursed for patients who have any of the following: 3.1. previously failed both cyclophosphamide and mycophenolate mofetil (or other forms of mycophenolate) induction therapies 3.2. an eGFR < 30 mL/min/1.73 m^2.	Patients who previously failed both cyclophosphamide and mycophenolate mofetil (or other forms of mycophenolate) induction therapies and patients who had an eGFR < 30 mL/min/1.73 m^2 at the screening visit were excluded from the BLISS-LN trial	—
4. The maximum duration of initial authorization is 12 months.	The BLISS-LN trial reported a statistically significant difference in PERR outcome at week 52.	—
Renewal		
5. For renewal after initial authorization, the physician must provide proof of beneficial clinical effect when requesting continuation of reimbursement, defined as all of the following: 5.1. reduction in glucocorticoids to ≤ 7.5 mg/day after 12 months of therapy 5.2. an estimated eGFR that is no	The BLISS-LN PERR composite end points required a decrease in proteinuria, limited worsening of eGFR, and not meeting treatment failure criteria (of which failure to reduce steroids was 1 criterion).	CDEC noted that after the first 12 months of therapy with belimumab, patients whose OCS dose remained higher than 7.5 mg/day of prednisone or its equivalent, but their OCS dose decreased by at least 50% from baseline could be considered as having achieved the OCS dose reduction condition.

Reimbursement condition	Reason	Implementation guidance
more than 20% below the value before the renal flare (preflare value) or ≥ 60 mL/min/1.73 m^2 after 12 months of therapy.		
6. The physician must also provide proof of improvement in proteinuria defined as either: 6.1. proteinuria no greater than 0.7 g/24 hours after 12 months of therapy if baseline proteinuria is < 3.5 g/24 hours 6.2. proteinuria no greater than 0.7 g/24 hours after 18 to 24 months of therapy if baseline proteinuria is in the nephrotic range (i.e., > 3.5 g/24 hours).	The clinical expert and the most recent KDIGO and EULAR/ERA–EDTA clinical practice guidelines for LN suggest that a complete response to therapy should aim for proteinuria of < 0.5 g/24 hours to < 0.7 g/24 hours within 12 months of initiating therapy (but some people with nephrotic range proteinuria may require an additional 12 months) plus stabilization or improvement in eGFR within 10% to 15% of baseline (i.e., preflare).	—
7. For subsequent renewal, the physician must provide proof that the initial response achieved after the first 12 months of therapy with belimumab has been maintained. Subsequent renewals should be assessed annually.	Ensure patients are maintaining their response to treatment with belimumab.	—
Discontinuation		
8. Treatment with belimumab must be discontinued if the patient does not meet all of the renewal criteria or if the patient has any of the following: 8.1. an eGFR decrease to less than 30 mL/min/1.73 m^2 8.2. the addition of other immunosuppressant agents (other than as part of the induction and maintenance regimens), corticosteroid use outside of the limits, anti–tumour necrosis factor therapy, or other biologics.	Patients who had an eGFR < 30 mL/min/1.73 m^2 at the screening visit were excluded from the BLISS-LN trial and there were no data to suggest whether belimumab might be effective in these patients. In the BLISS-LN trial, prohibited medications included new immunosuppressant agents (other than as part of the induction and maintenance regimens), corticosteroid use outside of the limits, other investigational agents (biologic or nonbiologic), anti–tumour necrosis factor therapy (e.g., adalimumab, etanercept, infliximab), other biologics (e.g., rituximab, abatacept), IV immunoglobulin, or plasmapheresis.	—
Prescribing		
9. The patient should be under the care of either a rheumatologist or a nephrologist experienced in the management of LN	Accurate diagnosis and follow-up of patients with LN is important to ensure that belimumab is prescribed to the most appropriate patients.	—

Reimbursement condition	Reason	Implementation guidance
Pricing		
10. A reduction in price	The ICER for belimumab plus MMF is $352,880 per QALY when compared with MMF alone. A price reduction of at least 58% for belimumab would be required for belimumab plus MMF to be able to achieve an ICER of $50,000 per QALY compared with MMF alone.	—

eGFR = estimated glomerular filtration rate; EULAR/ERA–EDTA = European League Against Rheumatism and European Renal Association–European Dialysis and Transplant Association; ICER = incremental cost-effectiveness ratio; KDIGO = Kidney Disease Improving Global Outcomes; LN = lupus nephritis; MMF = mycophenolate mofetil, OCS = oral corticosteroid; PERR = primary efficacy renal response; QALY = quality-adjusted life-year.

Discussion Points

- CDEC discussed that when a flare of LN occurs, re-induction therapy is required; however, there is no evidence of belimumab's efficacy in subsequent treatment episodes or with other combinations of standard induction therapy.
- The clinician and patient group input indicated that patients would like to experience fewer flares and noted that flares have been associated with worse outcomes, increasing the risk of progression to end-stage renal disease (ESRD) and dialysis among patients with LN. CDEC discussed that in the BLISS-LN study, patients in the belimumab group experienced fewer severe flares as classified by the Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA)-SLEDAI Flare Index (SFI) and had a lower risk of experiencing a severe flare as classified by the SFI than those in the placebo group; however, the outcome of severe flare as classified by the SFI was considered supportive in the BLISS-LN study and was not adjusted for multiple statistical testing.
- The clinical expert noted to CDEC that patients who are gradually improving should wait for a maximum of 2 to 3 months to assess response to standard-of-care treatment before initiating belimumab. CDEC noted, based on the trial, there is no evidence for waiting to initiate belimumab.
- The clinical expert noted to CDEC that the optimal duration of maintenance therapy is unknown, but maintenance treatment should be continued for at least 3 to 5 years in those patients who achieve a complete response and potentially indefinitely in patients who have a partial response. CDEC discussed that it is still unknown how long patients should receive belimumab as maintenance therapy because the BLISS-LN study was only 2 years long, thus this remains an evidence gap.
- Health Canada has authorized both IV and subcutaneous (SC) formulations of belimumab for LN; however, the clinical and economic evidence available for patients with active LN is for the IV formulation only, and the SC formulation indication was based on extrapolated data. CDEC discussed that although the SC formulation may provide some benefits to patients in terms of decreased infusion centre visits and improved convenience, the evidence of equivalence between IV and SC formulations remains unclear.
- CDEC discussed the differing standard-of-care treatments currently used in practice (cyclophosphamide followed by azathioprine or MMF) and the underlying uncertainty

in the economic evidence. Although a price reduction of at least 58% for belimumab was noted, given the reported uncertainty, a higher price reduction of up to 73% may be required, especially when considering patients treated with cyclophosphamide followed by azathioprine.

Background

Lupus is an autoimmune disease characterized by inflammatory processes that can occur in various tissues and organs of the body. A common form of lupus is systemic lupus erythematosus (SLE), which has an estimated prevalence of about 1 in 2,000 individuals in Canada. The age of onset is primarily between 16 and 55 years, and it occurs more often in females than in males (9:1). According to UpToDate Epidemiology and pathogenesis of SLE, published in June 2022, the median ages at diagnosis for white females range from 37 to 50 years, in white males from 50 to 59 years, in Black females from 15 to 44 years, and in Black males from 45 to 64 years. Kidney injury is common in SLE; LN occurs in approximately 50% of patients with SLE, usually within 5 years of an SLE diagnosis. Kidney involvement can remain silent or asymptomatic for a significant period of time; however, patients may experience fatigue, joint and muscle pain, edema, rash, and a variety of other symptoms. The disease is associated with substantial morbidity; serious complications include progression to ESRD, which requires dialysis or kidney transplant.

Treatment options for class III, IV, and/or V active LN include a high-dose corticosteroid that is tapered down over time and immunosuppressive agents such as MMF or mycophenolic acid, cyclophosphamide, or azathioprine. The clinical expert for this review noted that other treatments in addition to standard of care for patients with an inadequate response to first-line induction therapy may include rituximab, cyclosporin, or tacrolimus. The clinical expert for this review stated that in all cases of class III, IV, and/or V active LN, off-label use of antimalarials (i.e., hydroxychloroquine), bone protection (vitamin D, calcium, possibly antiresorptive agents), immunizations with non-live vaccines, and adjunct treatment with renin-angiotensin blockade and statins should be considered.

Belimumab has been approved by Health Canada in addition to standard therapy for treatment of active LN in adult patients. Belimumab is a monoclonal antibody. It is available as an IV infusion; the dosage recommended in the product monograph is 10 mg/kg, administered over an hour, at 2-week intervals for the first 3 doses and at 4-week intervals thereafter. Belimumab is also available as a solution for SC injection; the dosage recommended in the product monograph is 400 mg (two 200 mg injections) once weekly for 4 doses, then 200 mg once weekly thereafter. The product monograph indicates that the infusion rate may be slowed or interrupted if the patient develops an infusion reaction. In the event of a serious infusion-related or hypersensitivity reaction (e.g., anaphylaxis), treatment should be discontinued immediately and appropriate therapy should be administered. The Health Canada–recommended dose for SC injection is 400 mg (two 200 mg injections) once weekly for 4 doses, then 200 mg once weekly thereafter. For adult patients with LN transitioning from belimumab IV therapy to SC therapy, the first SC dose is to be administered 1 to 2 weeks after the last IV dose. This transition can occur any time after the patient completes the first 2 IV doses. The product monograph further states that belimumab should be used in combination with corticosteroids and mycophenolate or cyclophosphamide for

induction, or mycophenolate or azathioprine for maintenance, and the patient's condition should be evaluated continuously.

Sources of Information Used by the Committee

To make their recommendation, the committee considered the following information:

- a review of 1 placebo-controlled, double-blind, randomized controlled trial and 1 open-label extension study in adult patients with class III, IV, and/or V active LN
- patients' perspectives gathered by patient groups: Arthritis Consumer Experts, Lupus Ontario, a joint submission from the Kidney Foundation of Canada and Lupus Canada, and a cooperative submission from the Canadian Arthritis Patient Alliance, the Arthritis Society, the Canadian Skin Patient Alliance, and CreakyJoints
- input from public drug plans that participate in the CADTH review process
- input from 1 clinical specialist with expertise diagnosing and treating patients with active LN
- input from 1 clinician group: the Canadian Network for Improved Outcomes for Systemic Lupus Erythematosus
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

Patient Input

Four responses to CADTH's call for patient input for the belimumab submission were received. These consisted of submissions from Arthritis Consumer Experts, Lupus Ontario, a joint submission from the Kidney Foundation of Canada and Lupus Canada, and a cooperative submission from the Canadian Arthritis Patient Alliance, the Arthritis Society, the Canadian Skin Patient Alliance, and CreakyJoints. Patient input was gathered from surveys, video interviews, and focus group discussions among patients with lupus across Canada: 34 respondents (88% female) from Arthritis Consumer Experts, 10 respondents (90% female) with SLE from Lupus Ontario, 38 respondents (73% with LN and approximately 15% caregivers) from the Kidney Foundation of Canada and Lupus Canada. The cooperative submission conducted a focus group of 3 patients with LN as well as a video interview with 1 patient. The submission from Arthritis Consumer Experts also conducted an in-depth interview with 1 patient. A total of 17 patients (6 from a previous survey) in the included submissions had experience with the treatment under review.

Patients reported managing SLE was difficult given the severity of the physical symptoms, such as debilitating fatigue, joint pain, flares, skin rashes, nausea, loss of appetite, bruising, back pain, brain fog, mobility issues, and mental health issues. Respondents reported that currently available treatments are difficult to tolerate because of the many side effects. In their descriptions of their experiences with the current drug under review, patients reported both positive and negative outcomes. Some patients described experiencing side effects, such as severe allergic reaction, extreme nausea, sleep deprivation, frequent urinary tract

infections, depression, and psychosis. Other patients reported an overall decrease in their disease symptoms and improvement in physical ability, leading to improvement in their HRQoL.

The key outcomes patients would like to see addressed by a new therapy are reduction of side effects and number of medications used; reduction in fatigue, flares, pain, and rash and skin irritations; increased mobility and participation in physical activities; overall improvement in HRQoL; improved engagement in social activities; and affordability of medication.

Clinician Input

Input From Clinical Expert Consulted by CADTH

According to the clinical expert consulted by CADTH for this review, response to current standard-of-care induction therapy is suboptimal (only 20% to 35% of patients achieve a CRR within 6 to 12 months after initiation of induction therapy; of those who do respond, 20% to 35% relapse within 3 to 5 years), indicating a major unmet need because up to 40% of patients with LN can develop chronic kidney disease and progress to ESRD that requires dialysis or a transplant. Other unmet needs include lack of adherence, side effects (e.g., prednisone), and recurrent flares that cause progressive organ damage; in addition, only a few treatments are safe during pregnancy for a disease that largely affects those who can become pregnant. Currently, no treatments provide a long-term cure or long-term medication-free survival. According to the clinical expert, the current place in therapy for belimumab would be as add-on therapy to existing standard-of-care therapy (i.e., glucocorticoids and MMF or mycophenolic acid or cyclophosphamide) in patients with class III or IV (with or without class V) or pure class V active LN who have not attained an adequate renal response after 2 to 3 months of induction therapy. However, the clinical expert noted that the time to initiate belimumab may vary from start of induction therapy to 3 to 6 months after initiation of induction therapy depending on disease severity, patient response, and expert physician judgment. Other factors that may identify patients with active disease who may be most likely to respond to belimumab include:

- patient has had previous episodes of class III (with or without class V) or IV (with or without class V) or class V LN and another flare may cause a serious decline in renal function
- patient has active class III or IV (with or without class V) or class V LN with chronically impaired renal function
- patient is unable to decrease prednisone to 7.5 mg/day or less after 3 to 6 months of induction
- patient has extrarenal manifestations in addition to LN.

The clinical expert identified those patients who are least likely to benefit from belimumab are those with active LN who are not currently receiving standard-of-care induction therapy, those who have previously failed induction therapy with both MMF or mycophenolic acid and cyclophosphamide agents, and those with an eGFR of 30 mL/min/1.73 m^2 or less (it is unknown if belimumab would be efficacious in these patients because they were excluded from the BLISS-LN trial). In addition, patients who have attained a CRR after 6 to12 months of induction therapy will probably derive little incremental benefit from belimumab as an add-on to standard of care and should not be considered as candidates for belimumab.

In the opinion of the clinical expert, a clinically meaningful response to belimumab would include, in order of occurrence, at least a 25% reduction in proteinuria (as defined by the urine protein/creatine ratio [uPCR]) after 3 months of induction therapy, at least a 50% reduction in proteinuria after 6 months of therapy, a reduction in corticosteroids to 7.5 mg/day or less after 6 to 12 months of therapy, proteinuria no greater than 0.5 g/24 hours to 0.7 g/24 hours after 12 months of therapy (the response time can be delayed to 18 to 24 months if baseline proteinuria is in the nephrotic range; i.e., > 3.5 g/24 hours), and an estimated eGFR no more than 10% to 20% of preflare value and 60 mL/min/1.73 m^2 or higher after 12 months of therapy.

Clinician Group Input

The Canadian Network for Improved Outcomes for Systemic Lupus Erythematosus and 31 associated physicians provided input for this review.

The clinician group and physicians agreed that there have been some treatment gaps and unmet needs in the current LN therapeutics. These unmet needs include inability to achieve complete remission from currently existing treatment options (e.g., MMF and cyclophosphamide), increased risk for multiple complications from moderate or high doses of glucocorticoids, subsequent ESRD and renal replacement therapy associated with disease flares, and difficulty in maintaining adherence.

The clinician group and physicians indicated that a clinically meaningful response to treatment would include any of the following: complete remission (proteinuria < 0.5 g/24 hours) within 12 months of starting treatment, reduction in daily prednisone dose to levels less than 7.5 mg per day, or the reduction of the frequency and intensity of flares. According to the clinician group, sufficient time (at least 12 months) should be allowed for these outcomes to be observed and treatment should be discontinued after 12 months in cases in which no response can be demonstrated. The input stated that belimumab is expected to cause a shift in the current treatment paradigm for LN by addressing the disease mechanism. Its ability to modulate the maturation and functional differentiation of B cells, which produce autoantibodies that are central in SLE pathogenesis and tissue damage, renders it most suitable for patients who have not achieved at least partial remission, patients experiencing early and frequent flares, patients with steroid-dependent disease, and patients with adherence issues.

Drug Program Input

Input was obtained from the drug programs that participate in the CADTH Reimbursement Review process. The following were identified as key factors that could potentially affect the implementation of a CADTH recommendation for belimumab:

- relevant comparators
- considerations for initiation of therapy
- considerations for continuation or renewal of therapy
- considerations for discontinuation of therapy
- considerations for prescribing of therapy
- generalizability of trial populations to the broader populations in the jurisdictions
- system and economic issues.

The clinical expert consulted by CADTH provided advice on the potential implementation issues raised by the drug programs.

Table 2: Responses to Questions From the Drug Programs

Implementation issues	Response
Relevant comparators	
The clinical trial BLISS-LN looked at belimumab in combination with standard of care vs. placebo. Is placebo an appropriate comparator?	CDEC agreed with the clinical expert consulted by CADTH that placebo in addition to standard of care is an appropriate comparator for the indicated population because there are no other applicable comparators.
Considerations for initiation of therapy	
In BLISS-LN, standard-of-care induction therapy was initiated at any time within the 60 days before the day 1 baseline visit. Would this be an appropriate duration of time to assess response to standard of care?	The clinical expert noted that the efficacy and safety of initiating belimumab anytime within the 60-day window after initiation of standard-of-care induction therapy has been demonstrated in the BLISS-LN trial. In the trial, belimumab was initiated within 4 weeks after initiation of induction therapy in 82.5% of patients and, within 2 weeks after initiation of induction therapy in 57.6% of patients. However, because 20% to 35% of patients will respond adequately to standard-of-care induction therapy alone and the significant medication burden associated with standard-of-care induction therapy, the clinical expert noted that it would be prudent to wait a maximum of 2 to 3 months in patients who are gradually improving to assess response to standard of care before initiating belimumab. This should be a sufficient time to allow for a response to be seen, but not prolong an ineffective treatment and risk increasing renal damage. If response is deemed inadequate after 2 to 3 months, belimumab can be initiated. However, should the patient's condition worsen or the patient demonstrates no improvement within 2 to 4 weeks after initiation of standard-of-care induction therapy, it would be appropriate to initiate belimumab earlier in the induction course, either at the time of initiation of induction or within 1 month after initiation of induction (as was the case for most patients in BLISS-LN). The clinical expert noted that BLISS-LN did not assess the efficacy of administering belimumab later in the induction phase (i.e., after > 60 days of induction therapy). The expert noted that for patients who show some initial response within the first 2 to 3 months of induction therapy and then plateau or deteriorate or are unable to decrease steroids between months 3 to 6, there may be benefit in adding belimumab at 3 to 6 months after induction therapy to standard of care (although there are no data from the trial addressing this use of belimumab). Hence, the clinical expert noted that it may be appropriate to provide the prescriber the flexibility to initiate belimumab anytime from start of standard-of-care induction therapy to within the first 3 to 6 months after initiation of standard-of-care induction therapy, based on the judgment of the clinician expert. Because there is no evidence available regarding early vs. late initiation of belimumab compared with standard induction therapy, CDEC recommended that, to be eligible for belimumab, patients must have started standard induction therapy within the previous 60 days as per the inclusion criteria of the BLISS-LN trial.

Implementation issues	Response
How is it determined if patients are not responding or refractory to standard of care?	The clinical expert noted that a clinically meaningful response to standard of care would include, in order of occurrence, at least a 25% reduction in proteinuria (as defined by uPCR) after 2 to 3 months of therapy, at least a 50% reduction in proteinuria after 6 months of therapy, reduction in glucocorticoids to ≤ 7.5 mg per day after 6 to 12 months of therapy, proteinuria no greater than 0.5 to 0.7 g/24 hours after 12 months of therapy (the response time can be delayed to 18 to 24 months if baseline proteinuria is in the nephrotic range; i.e., > 3.5 g per 24 hours), an estimated eGFR no more than 10% to 20% of preflare value and ≥ 60 mL/min/1.73 m^2 after 12 months of therapy. These response criteria would also apply to treatment with belimumab in addition to standard of care. CDEC noted that to be considered a responder, a patient must have all of the following: • a reduction in glucocorticoids to ≤ 7.5 mg/day after 12 months of therapy • an estimated eGFR that is no more than 20% below the value before the renal flare (preflare value) or ≥ 60 mL/min/1.73 m^2 after 12 months of therapy • an improvement in proteinuria, defined as either ◦ proteinuria no greater than 0.7 g/24 hours after 12 months of therapy if baseline proteinuria is < 3.5 g/24 hours ◦ proteinuria no greater than 0.7 g/24 hours after 18 to 24 months of therapy if baseline proteinuria is in the nephrotic range (i.e., > 3.5 g/24 hours).
What is an appropriate trial of standard of care before the addition of belimumab?	The clinical expert stated that standard of care should be trialled for a maximum of 2 to 3 months to determine if the patient is responding and is able to tolerate the medication burden. The clinical expert noted that it would also be appropriate to initiate treatment with belimumab at the same time as initiation of standard of care if the patient is rapidly worsening or showing no improvement. Given that there is no evidence regarding early vs. late initiation of belimumab compared with standard induction therapy, CDEC recommended that, to be eligible for belimumab, patients must have started standard induction therapy within the previous 60 days as per the inclusion criteria of the BLISS-LN trial.
How should standard of care be defined? As in what is an appropriate dose of daily glucocorticoid that would be considered appropriate for induction therapy? Maintenance therapy?	CDEC agreed with the clinical expert consulted by CADTH that an appropriate dose of daily glucocorticoid for induction therapy includes 500 mg/day to 1,000 mg/day of IV methylprednisolone for 3 days, followed by daily oral prednisone (0.5 mg/kg to 1 mg/kg). It is recommended that glucocorticoids be gradually tapered and discontinued over 1 to 2 years; however, if glucocorticoids are continued, the dose should not exceed 5 mg/day to 7.5 mg/day (prednisone equivalent) due to their substantial long-term toxicity. The optimal duration of maintenance therapy is unknown, but it should be continued for at least 3 to 5 years in those patients who achieve a complete response and potentially indefinitely in those with a partial response.
The product monograph notes that, in active LN, belimumab should be used in combination with corticosteroids and mycophenolate mofetil or cyclophosphamide for induction or mycophenolate mofetil or azathioprine for maintenance.	The clinical expert noted to CDEC that if a patient is refractory or not responding to standard-of-care induction therapy after 2 to 3 months, options include switching to an alternative induction therapy (i.e., mycophenolate mofetil to cyclophosphamide or cyclophosphamide to mycophenolate). Cyclophosphamide is associated with infertility, and the clinical expert stated

Implementation issues	Response
For patients who are refractory to treatment or patients who are not responding to standard-of-care induction therapy as defined above, should additional agents be trialled (i.e., alternate mycophenolate mofetil, cyclophosphamide and azathioprine combination and/or calcineurin inhibitors, or rituximab)? Should any of these alternatives be trialled before belimumab is added on to standard of care? What is an appropriate trial period of these medications? For patients for whom these therapies are not appropriate, is monotherapy with belimumab an option?	that if belimumab were available to the prescriber, addition of belimumab to mycophenolate would be preferred to switching from mycophenolate to cyclophosphamide. A calcineurin inhibitor (i.e., cyclosporin or tacrolimus) or rituximab can also be used with mycophenolate, but usage is off-label and there is limited evidence supporting this approach; guidelines recommend these as add-on only in refractory cases. Rarely, rituximab can be combined with cyclophosphamide for induction. Azathioprine would very rarely be used as induction therapy because it is less efficacious than mycophenolate or cyclophosphamide. In summary, if a patient does not respond rapidly to induction with mycophenolate, addition of belimumab to mycophenolate would be the preferred option. CDEC agreed with the clinical expert consulted by CADTH that monotherapy with belimumab is not an appropriate therapy for induction or maintenance therapy in LN. In the BLISS-LN trial, belimumab was administered with standard of care and has never been studied as monotherapy for LN.
What is the appropriate place in therapy for belimumab (i.e., after 6 to 12 months of standard of care, before calcineurin inhibitors and/or rituximab)?	The clinical expert noted that standard of care (i.e., glucocorticoids and mycophenolate mofetil, mycophenolic acid, or cyclophosphamide) for induction therapy should be trialled for a maximum of 3 to 6 months (refer to previous discussion regarding why adding on belimumab up to 6 months after initiation of standard-of-care induction may be appropriate) to determine if the patient is responding to treatment before adding on belimumab. The clinical expert also noted that it would also be appropriate to initiate treatment with belimumab immediately alongside existing standard of care for patients with worsening renal parameters or with no improvement within 2 to 4 weeks after initiating induction. Given that there is no evidence comparing early vs. late initiation of belimumab with standard induction therapy, CDEC recommended that, to be eligible for belimumab, patients must have started standard induction therapy within the previous 60 days as per the inclusion criteria of the BLISS-LN trial.
Considerations for continuation or renewal of therapy	
Are the composite end points of PERR in the BLISS-LN trial appropriate to assess response to therapy?	CDEC agreed with the clinical expert consulted by CADTH that the outcomes used in clinical practice align with those used in the trial and these indicators would not vary much across physicians.
The sponsor notes that eGFR and proteinuria changes are predictive of renal survival. Does this outcome appropriately measure response to drug therapy over time, given the waxing and waning nature of the condition?	CDEC agreed with the clinical expert consulted by CADTH that these outcomes are appropriate measures of response to therapy over time. Treatment goals include attaining proteinuria levels ≤ 0.7 g/24 hours and eGFR levels ≥ 60 mL/min/1.73 m^2. Not attaining or maintaining these levels over time suggests the patient is not responding to therapy, and this therapy should not be renewed and another therapy should be tried.
It may be difficult for jurisdictions to assess response to therapy at a given point in time. Is there any point in time that disease control would be appropriately measured?	The clinical expert commented that renewal should be on annual basis, with treatment discontinued if the patient is not responding after the first 6 to 12 months (the response time can be delayed to 18 to 24 months if baseline proteinuria is in the nephrotic range; i.e., > 3.5 g/24 hours). The clinical expert noted that in BLISS-LN, the percentage of patients in both treatment groups who achieved the primary outcome over time was identical through to week 20 after randomization (n = 78, 35.0% in each treatment group) and started to diverge (with a greater percentage achieving PERR in the belimumab group) at week 24 through to week 104. Hence, it would be appropriate to wait at

Implementation issues	Response
	least 6 months to assess response to belimumab; in patients with higher levels of proteinuria, the clinical expert believed it would be appropriate to wait up to 12 months to determine if the response is sufficient to warrant continuation. CDEC recommended that treatment response be assessed 1 year after initiation of treatment with belimumab, except for patients whose baseline proteinuria is in the nephrotic range (i.e., > 3.5 g/24 hours); such patients should attain proteinuria levels ≤ 0.7 g/24 hours within 18 to 24 months after initiation of treatment with belimumab to be considered responders.
Is a glucocorticoid dose less than or equal to 10 mg/day clinically meaningful for these patients?	CDEC agreed with the clinical expert consulted by CADTH that during maintenance therapy it is recommended that glucocorticoids be gradually tapered and discontinued; however, if glucocorticoids are continued, the dose should not exceed 5 mg/day to 7.5 mg/day (prednisone equivalent) due to their substantial long-term toxicity.
Considerations for discontinuation of therapy	
BLISS-LN evaluated the primary efficacy renal response at week 104 (2 years). What is the appropriate time frame to assess patients for treatment response?	The clinical expert stated that initial approval should be for 2 years. Treatment with belimumab should be discontinued after the first 6 to 12 months if there is inadequate response or improvement based on clinician judgment. The clinical expert also noted that it would be appropriate to wait at least 6 months to assess the response to belimumab; in patients with higher levels of proteinuria, the clinical expert believed it would be appropriate to wait up to 12 months to determine if the response is sufficient to warrant continuation. CDEC recommended that treatment response be assessed 1 year after initiation of treatment with belimumab, and treatment response should be assessed annually thereafter. Patients whose baseline proteinuria is in the nephrotic range (i.e., > 3.5 g/24 hours) should attain proteinuria levels ≤ 0.7 g/24 hours within 18 to 24 months after initiation of treatment with belimumab to be considered responders, and then treatment response should be assessed annually thereafter.
The sponsor is recommending that treatment with belimumab plus standard of care be discontinued if no improvements of disease activity and/or symptoms are observed after 6 months. What would be appropriate clinical markers of disease activity to demonstrate improvements in disease activity or symptoms at 6 months?	The clinical expert indicated that a partial renal response is a reasonable clinical marker of disease activity to demonstrate improvement at 6 months, which is defined as reduction in proteinuria to at least 50% and to < 3 g/24 hours if baseline was > 3 g/24 hours, and stabilization or improvement in eGFR within 20% of baseline (i.e., before onset of LN). CDEC noted specific response criteria with annual approval at 12 months should allow enough time to determine if therapy is working.
Considerations for prescribing of therapy	
Who would be most appropriate to prescribe belimumab for this indication? Would it be rheumatologists or nephrologists?	CDEC agreed with the clinical expert consulted by CADTH that the diagnosis, treatment, and monitoring of patients with LN who might receive belimumab should be by a specialist, either a rheumatologist or a nephrologist experienced in the management of LN.
Is there a difference in clinical benefit between the IV and subcutaneous treatments?	CDEC agreed with the clinical expert consulted by CADTH that it is currently unknown if there is a different clinical benefit between the IV and subcutaneous treatment for the indicated population.

Implementation issues	Response
Generalizability	
For patients for whom mycophenolate mofetil, or mycophenolic acid, or cyclophosphamide are not appropriate, is monotherapy with belimumab an option?	CDEC agreed with the clinical expert consulted by CADTH that monotherapy with belimumab is not an option for the indicated population because belimumab was only assessed as an add-on to standard of care with either mycophenolate or cyclophosphamide in BLISS-LN.
Would belimumab be used to treat patients who are younger than 18 years?	CDEC agreed with the clinical expert consulted by CADTH that there is no current clinical data to support the use of belimumab to treat patients younger than 18 years of age with LN. In addition, belimumab is not approved by Health Canada in patients who are younger than 18 years of age.
Would patients with class I, II, and VI LN be treated with belimumab?	CDEC agreed with the clinical expert consulted by CADTH that patients with class I (minimal mesangial), II (mesangial proliferative), and VI (advanced sclerotic) LN generally do not require immunosuppressive therapy and would not be treated with belimumab.
Patients with severe active renal lupus were excluded from the clinical trial. Would such patients be treated with belimumab? Are there additional treatment options used to control the disease in these patients?	CDEC agreed with the clinical expert consulted by CADTH that patients with severe impairment in eGFR (< 30 mL/min) were excluded from BLISS-LN and that there are no data to suggest whether belimumab might be effective in these patients. In such patients with refractory disease, there is no evidence supporting alternative therapies. Rituximab may be combined with mycophenolate or cyclophosphamide as salvage therapy.
There are no Canadian-specific guidelines for management of LN. Is the international system that stratifies LN into 6 classes (I to VI) used routinely in Canada? Would it be practical to incorporate this staging classification system in reimbursement criteria (i.e., is this used in clinical practice)?	CDEC agreed with the clinical expert consulted by CADTH that the 2003 ISN/RPS classification of LN that stratifies LN into 6 classes (I to VI) is routinely used in Canadian clinical practice and would be practical to incorporate into the reimbursement criteria.
System and economic issues	
Rituximab biosimilars have undergone pricing negotiations through pCPA.	Comment from the drug programs to inform CDEC deliberations.
There may be potential savings if the drug prevents or delays patients accessing dialysis.	CDEC noted that it is currently unknown whether there will be savings due to the absence of long-term evidence to indicate treatment with belimumab would prevent or delay progression to kidney failure.

CDEC = CADTH Canadian Drug Expert Committee; ISN = International Society for Nephrology; LN = lupus nephritis; pCPA = pan-Canadian Pharmaceutical Alliance; RPS = Renal Pathology Society; uPCR = urine protein/creatinine ratio.

Clinical Evidence

Pivotal Studies and Protocol-Selected Studies

Description of Studies

One double-blind placebo-controlled, phase III trial RCT (BLISS-LN) was included in this review (166 sites in 21 countries; N = 448) that evaluated the efficacy, safety, and tolerability of an IV treatment regimen of belimumab 10 mg/kg in adult patients with class III or IV (with or without the presence of class V) or pure class V active LN while receiving standard of care.

The primary objective was to evaluate the effect of belimumab 10 mg/kg compared with placebo in renal response as measured by the difference in the proportion of patients who achieved a PERR at week 104. PERR was a dichotomous composite outcome (responder vs. nonresponder) that was considered achieved when all 3 of the following components were met: uPCR of 0.7 or less, eGFR no greater than 20% below preflare value or 60 mL/min/1.73 m^2 or more and not a treatment failure (i.e., patients who did not take a protocol-prohibited or -restricted medication or a protocol-prohibited dose). A responder was defined by a response at the week 48 or week 100 visit that was confirmed by a repeat measure at the week 52 or week 104 visit, respectively. The key secondary objectives were to evaluate the effect of belimumab 10 mg/kg compared with placebo on CRR at week 104, PERR at week 52, time to renal-related event or death, and ORR at week 104. CRR was a composite outcome that was considered achieved when all 3 of the following components were met: uPCR was 0.5 or less, eGFR was no more than 10% below preflare value or within the normal range at 90 mL/min/1.73 m^2 or higher, and not a treatment failure (i.e., patients did not take a protocol-prohibited or -restricted medication or a protocol-prohibited dose). A response was defined as a response at the week 100 visit confirmed by a repeat measurement at the week 104 visit. ORR was an outcome in which patients achieved a CRR, partial renal response, or no response. Treatment failure was defined as violating the corticosteroid rules (i.e., failed to taper corticosteroids to ≤ 10 mg/day by week 24 and not exceed this dose of 10 mg/day through week 104); receiving additional immunosuppressive agents (except topical agents) beyond the induction and maintenance regimens; initiating the use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or antimalarial drugs after week 24; or the standard therapy (cyclophosphamide or azathioprine or MMF) exceeded permitted doses.

Baseline patient characteristics, including age, sex, and race were balanced between groups. Patients were predominantly female (88.3% in the belimumab group and 87.9% in the placebo group), a majority were Asian (51.1% in the belimumab group and 48.9% in the placebo group), followed by white (32.7% and 33.6%) and Black (13.5% and 13.9%), and 84% of patients in both the belimumab and placebo groups were categorized as renal biopsy class III or IV (with or without class V) according to the local reader. Disease characteristics, such as SLE and LN disease duration, mean score for the SLEDAI-S2K with modified scoring for proteinuria, mean eGFR, and mean uPCR were balanced between treatment groups at baseline. There were some baseline differences in use of concomitant medications between groups, including antimalarials (74.4% and 69.1%) as well as prednisone (steroids were converted to prednisone equivalent) with a mean dose of 66.5 mg/day (SD 99.6 mg/day) and 72.5 mg/day (SD 133.2 mg/day) for the belimumab and placebo groups, respectively. Patients also used immunosuppressants (88.8% in the belimumab group and 86.1% in the placebo group) and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (65.9% in the belimumab group and 67.3% in the placebo group) at baseline.

Efficacy Results

In the BLISS-LN study, the primary end point, PERR at week 104, was statistically significant in favour of belimumab 10 mg/kg group (43.0% vs. 32.3%) with an adjusted between–treatment group difference of 10.66% (95% confidence interval [CI], 1.89 to 19.42; P = 0.0311). In addition, statistically significant differences in favour of the belimumab 10 mg/kg group were reported for all key secondary end points of CRR at week 104 (30.0% vs. 19.7%) with an adjusted between-group difference of 10.27% (95% CI, 2.40 to 18.14; P = 0.0167); PERR at week 52 (46.6% vs. 35.4%) with an adjusted between–treatment group difference of 11.12% (95% CI, 2.25 to 19.99; P = 0.0245); ORR at week 104 (30.0% belimumab vs. 19.7% placebo achieving a complete response) with an adjusted between-group difference of 10.27% (95%

CI, 2.40 to 18.14; P = 0.0167); and time to renal-related event or death (15.7% belimumab vs. 28.3% placebo experiencing an event), with an HR of 0.51 (95% CI, 0.34 to 0.77; P = 0.0014).

Subgroup analyses based on baseline renal biopsy class (class III or class IV vs. class III plus class V or class IV plus class V vs. class V) and the induction regimen (cyclophosphamide vs. MMF) for the primary and the key secondary end points were generally consistent with the overall results for all subgroups except for the baseline renal biopsy class V subgroup and the cyclophosphamide and azathioprine subgroup, the results of which were not statistically significantly different between treatment groups. However, the study was not designed nor powered to evaluate efficacy in subgroups, and the small number of patients in the class V and the cyclophosphamide and azathioprine subgroups might have led to the lack of statistical significance between treatment groups.

In terms of secondary outcomes, a higher proportion of patients in the belimumab 10 mg/kg group compared with the placebo group received an average daily prednisone dose of 7.5 mg or less at week 104 since the previous 4 week visit (40.8% vs. 29.6%) with an odds ratio (OR) of 1.65 (95% CI, 1.11 to 2.45). In terms of disease activity, the least squares mean change from baseline in SLEDAI-S2K at week 104 was −7.7 (standard error [SE] = 0.46) in the belimumab group and −6.1 (SE = 0.47) in the placebo group with a least squares mean difference of −1.5 (95% CI, −2.4 to −0.6). The proportion of patients with a SLEDAI-S2K score less than 4 at week 104 was higher in the belimumab group compared with the placebo group (27.8% vs. 18.4%) with an OR of 1.76 (95% CI, 1.11 to 2.78). A higher proportion of patients experienced a severe flare postbaseline to week 104 in the placebo group (31.4%) than in the belimumab 10 mg/kg group (18.8%), and the risk of experiencing a severe flare at any time, based on the SFI, was lower in patients in the belimumab 10 mg/kg group compared with patients in the placebo group (HR = 0.57; 95% CI, 0.39 to 0.84).

There was no HRQoL data assessed in the BLISS-LN trial.

Harms Results

Rates of adverse events (AEs) were similar in both treatment groups (95.5% belimumab vs. 94.25% placebo). Frequent AEs that occurred more commonly in the belimumab 10 mg/kg group than in the placebo group were urinary tract infection (19.2% vs. 15.6%), cough (12.5% vs. 8.5%), and upper abdominal pain (6.3% vs. 2.7%). The number of patients experiencing at least 1 serious AE (SAE) was similar in both treatment groups (25.9% belimumab vs. 29.9% placebo). The most common SAEs were pneumonia (4.0% vs. 3.1%), herpes zoster (1.8% vs. 0.9%), gastroenteritis (0% vs. 2.2%), lung infection 0.9% vs. 1.3%), LN (0.4% vs. 1.8%), and urinary tract infection (1.3% vs. 0.9%). An equal percentage of withdrawals due to AEs occurred in the belimumab 10 mg/kg group and placebo group (12.9% vs. 12.9%); the most common reason for withdrawal in both groups was pneumonia (4.0% vs. 3.1%).

A total of 11 deaths occurred during the double-blind phase of the BLISS-LN trial, mainly due to infections. There were 6 (2.7%) deaths in the belimumab 10 mg/kg group and 5 (2.2%) deaths the placebo group.

Common notable harms in the BLISS-LN trial included postinfusion-related systemic reactions (11.6% belimumab vs. 12.9% placebo); serious infections of herpes zoster (2.2% vs. 0.9%), active tuberculosis (0.9% vs. 0.4%), and sepsis (0% vs. 0.4%); malignancies (including nonmelanoma skin cancer) (1.3% vs. 0%), and serious suicidal behaviour (0.4% vs. 0%).

Critical Appraisal

In terms of limitations, a greater proportion of patients discontinued from the placebo group than the belimumab group, which may have led to bias the results in favour of belimumab. However, the sensitivity analyses that assessed the impact of missing data showed results that were generally supportive of the primary analysis. Regarding calculations of patients' average daily prednisone dose in the BLISS-LN trial, days when a patient did not have a prednisone dose recorded were considered as 0 mg for the day in the calculation, which would likely have underestimated the average dose of prednisone used in the study and may also have led to bias, although the direction of bias is unknown. Improvements in HRQoL were identified as important outcomes by the patient groups who provided input for this review. However, there were no HRQoL data collected in the BLISS-LN trial, hence it is unknown what impact belimumab would have on HRQoL.

The product monograph for belimumab authorized both IV and SC formulations for LN. However, the approval of SC formulations was based on extrapolated data, and there is no clinical evidence regarding the SC formulation for patients with active LN.

Overall, the clinical expert consulted felt the characteristics of the patient population enrolled in the trials was a good representation of the target population. The clinical expert did not identify any issues with the use of concurrent treatments or conduct of the trial that could substantially affect the generalizability of the findings.

Indirect Comparisons

No indirect evidence was available.

Other Relevant Evidence

Data from 1 open-label extension (OLE) study was summarized in this report.

Description of Study

The OLE study provided supplemental safety and efficacy data for patients who received IV belimumab 10 mg/kg plus standard-of-care therapy for up to 28 weeks (N = 254) among eligible patients who completed all assessments at week 104 in the BLISS-LN trial. Patients received their first dose at week 104 of the double-blind phase of the BLISS-LN trial (marked as day 0 for the open-label phase). There were 2 groups in the extension phase: a placebo-to-belimumab group (patients switched from placebo to belimumab) and a belimumab-to-belimumab group (patients remained on belimumab). Criteria for the open-label phase allowed for the use of concomitant medications, including immunosuppressants and corticosteroids, which were prohibited in the BLISS-LN trial. Also, PERR and CRR were evaluated based on observed data at weeks 12, 24, and 28 of the open-label study and criteria were required to be met at a single time point only, meaning criteria did not have to be met on consecutive visits as was required for the double-blind phase of the BLISS-LN trial.

Efficacy Results

Results from the OLE study showed that the proportion of patients who achieved a PERR increased from baseline to week 28 in both the belimumab-to-belimumab group (from 71% to 75%) and the placebo-to-belimumab group (from 60% to 67%) using the open-label phase criteria. Post hoc analyses found that when using the pivotal trial–defined criteria for a PERR, the proportion of patients who achieved a PERR from baseline to week 28 decreased in the

belimumab-to-belimumab group (from 66% to 52%) and remained stable in the placebo-to-belimumab group (from 54% to 53%). Similar results were found for the proportion of patients who achieved a CRR. Reductions in PERR and CRR rates at week 28 in the open-label study for the belimumab-to-belimumab group were mainly due to discontinuations (n = 8) or intake of concomitant medications (n = 9) allowed during the OLE phase but counted as treatment failures for the post hoc statistical analysis. Median uPCR and eGFR remained similar at baseline and at week 28 in both groups. There were no marked changes in the proportions of patients with SLEDAI-S2K scores less than 4 or in the proportion of patients who received an average daily prednisone equivalent dose of 7.5 mg/day or less in either group from baseline to week 28.

Harms Results

The number of patients who experienced at least 1 AE in the open-label phase was higher in the belimumab-to-belimumab group (70%) than in the placebo-to-belimumab (62%) group. The most common AEs that occurred in at least 5% of patients in either group included infections and infestations (49% vs. 42%), musculoskeletal and connective tissue disorders (12% vs. 13%), skin and subcutaneous tissue disorders (13% vs. 8%), gastrointestinal disorders (10% vs. 9%), and respiratory, thoracic, and mediastinal disorders (11% vs. 4%) in the belimumab-to-belimumab and placebo-to-belimumab groups, respectively. The percentage of patients who experienced at least 1 SAE during the open-label phase was low (8% in the belimumab-to-belimumab group and 4% in the placebo-to-belimumab group). The percentage of withdrawals due to AEs was also very low in both groups (3% vs. 0.8%). Common notable harms included post–infusion systemic reactions (4% vs. 3%) and infections of special interest (opportunistic infections, herpes zoster, tuberculosis, sepsis) (5% vs. 2%) in the belimumab-to-belimumab and placebo-to-belimumab groups, respectively. Two cases of serious infections of special interest were reported in the belimumab-to-belimumab group: serious tuberculosis and serious disseminated herpes zoster. One case of suicidal behaviour occurred in a patient diagnosed with an adjustment disorder. This patient recovered and completed the treatment throughout the open-label phase. One death, deemed SLE-related, occurred during the open-label phase in the placebo-to-belimumab group.

Critical Appraisal

The extension study allowed for the investigation of long-term efficacy and harms of belimumab for an additional 28 weeks for eligible patients who completed the BLISS-LN trial. Because there was no active comparator and all outcomes were descriptive in nature, it is difficult to make any inferences regarding the results. Furthermore, extension studies are often limited by selection bias because only those patients who are tolerant to treatment and complete the parent studies are eligible to enrol into the OLE study. An additional limitation is the open-label nature of treatment, which can bias the reporting of subjective end points (i.e., harms). Finally, the relatively short duration of the OLE study is insufficient to observe whether an appreciable benefit was derived among those who had transitioned from placebo-to-belimumab group.

Economic Evidence

Table 3: Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	Adult patients with active LN
Treatment	Belimumab in combination with standard therapy (IV cyclophosphamide [CYC] for induction followed by azathioprine [AZA] for maintenance; or mycophenolate mofetil [MMF] monotherapy) • Belimumab plus CYC followed by AZA • Belimumab plus MMF
Dose regimen	IV: 10 mg per kg every 2 weeks for the first 3 doses, then every 4 weeks, in combination with standard therapy Subcutaneous: 200 mg once weekly, in combination with standard therapy
Submitted price	Belimumab: 120 mg in 5 mL vial lyophilized powder for IV infusion: $305.71 400 mg in 20 mL vial lyophilized powder for IV infusion: $1,091.01 200 mg in 1 mL for SC injection: $1,581.59 (1 pack of 4)
Treatment cost	Belimumab is an add-on therapy, costing an additional $20,631 to $25,938 per year
Comparator	Standard therapy • CYC followed by AZA • MMF
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (70 years)
Key data source	BLISS-LN evaluated the efficacy and safety of belimumab (IV, 10 mg/kg) plus standard therapy
Key limitations	• The sponsor did not consider the reimbursement request as a scenario analysis and the model was not sufficiently flexible to report the cost-effectiveness of belimumab plus standard therapy in the reimbursement request population; specifically, incorporating the criteria of patients who fail to respond to treatment within 6 months. • Due to the small number of patients, clinical subgroup data on CYC followed by AZA was insignificant and imprecise. Because the clinical subgroup data on CYC followed by AZA was used to derive the model transition probabilities, this propagated uncertainty into the modelled treatment effect of belimumab. Furthermore, modelling transitions between health states primarily based on levels of decline from baseline eGFR is likely an oversimplification of disease progression. • The model structure does not adequately reflect the management of active LN in Canadian clinical practice. Subsequent therapies after treatment discontinuation and/or having inadequate response to first-line therapy and long-term immunosuppressive therapy usage were not modelled. • The long-term efficacy of belimumab on reducing flare rates is unknown, and extrapolated data predicting long-term flares events for standard therapy were underestimated. • Utility values were informed by patients with CKD and may not be reflective of patients with active LN.

Component	Description
	• The cost-effectiveness model was overly complex and unstable. Vastly different ICERs were produced when the probabilistic analyses were run using the sponsor's suggested 1,000 iterations.
CADTH reanalysis results	• Due to the inappropriate model structure and limitations and uncertainty in the clinical data, CADTH was unable to derive a base-case analysis. Instead, an exploratory reanalysis was conducted that used more appropriate assumptions, although CADTH notes the magnitude of clinical benefit estimated for belimumab plus standard therapy in this reanalysis may be overestimated due to uncontrolled limitations. • In the CADTH exploratory reanalysis, the following changes were made: probabilistic analyses were run using 5,000 iterations and a generalized gamma curve was used to inform the time to first renal flare for belimumab and the comparator arm. • The CADTH exploratory reanalysis estimated that belimumab plus MMF was associated with an ICER of $352,880 per QALY gained (incremental costs = $201,083; incremental QALYs = 0.57) vs. MMF alone. Belimumab plus CYC followed by AZA was dominated (more costly, less effective) by belimumab plus MMF. • At a willingness-to-pay threshold of $50,000 per QALY, belimumab would require a price reduction of at least 58%, whereas belimumab plus CYC followed by AZA required a price reduction of 73% and belimumab plus MMF required a price reduction of 58%. However, given the uncertainties in the reanalysis, higher price reductions may be required to ensure the cost-effectiveness of belimumab plus standard therapy. • CADTH was unable to address cost-effectiveness of add-on belimumab in the reimbursement population, uncertainties in the modelled disease progression, a model structure that failed to adequately reflect the management of active LN in clinical practice, and utility values for LN patients. Therefore, the cost-effectiveness of add-on belimumab is uncertain.

AZA = azathioprine, CKD = chronic kidney disease; CYC = cyclophosphamide, ICER = incremental cost-effectiveness ratio; LN = lupus nephritis; LY = life-year; MMF = mycophenolate mofetil, QALY = quality-adjusted life-year.

Budget Impact

CADTH identified the following key limitations within the sponsor's BIA: proportion of patients eligible for belimumab treatment is uncertain, uncertainty in SC versus IV use of belimumab in Canadian clinical practice, proportion of patients requiring belimumab induction in year 1 was underestimated, and uncertainty in the proportion of patients requiring induction to re-establish remission. The CADTH reanalysis updated the proportion of patients expected to receive induction belimumab in year 1. In the CADTH base case, when considering belimumab as add-on treatment, the budget impact of reimbursement belimumab plus standard therapy is expected to be $2,796,447 in year 1, $4,884,617 in year 2, and $6,394,557 in year 3, for a 3-year expected budget impact of $14,075,621.

CDEC Information

Members of the Committee

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunsky, Mr. Morris Joseph, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Ms. Heather Neville, Dr. Danyaal Raza, Dr. Emily Reynen, and Dr. Peter Zed

Meeting date: November 24, 2022

Regrets: One expert committee member did not attend

Conflicts of interest: None