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CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

(Final)

BELIMUMAB (BENLYSTA SUBCUTANEOUS [SC] — GLAXOSMITHKLINE INC.)
Indication: Systemic lupus erythematosus (SLE).

RECOMMENDATION
The CADTH Canadian Drug Expert Committee (CDEC) recommends that belimumab SC should not be reimbursed for use in addition to standard therapy for reducing disease activity in adult patients with active, autoantibody-positive, SLE.

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Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that belimumab subcutaneous (SC) should not be reimbursed for use in addition to standard therapy for reducing disease activity in adult patients with active, autoantibody-positive, SLE.

Reasons for the Recommendation

1. In one 52-week double-blind, randomized controlled trial (RCT) that compared belimumab SC treatment to placebo in patients with active SLE on standard background therapy (the BLISS-SC study), a statistically significant greater proportion of belimumab SC-treated patients achieved a response based on the SLE responder index (SRI, 61% versus 48%; odds ratio [OR] 1.68, 95% confidence interval [CI], 1.25 to 2.25) and a smaller proportion of belimumab SC-treated patients experienced a severe flare (11% versus 18%; hazard ratio 0.51, 95% CI, 0.35 to 0.74). Despite being statistically significant, the improvement in the response rate (13% higher in belimumab SC-treated patients versus placebo-treated patients) was considered by CDEC to be relatively modest.
2. In the BLISS-SC study, belimumab SC treatment did not statistically significantly reduce the proportion of patients who were able to reduce the dose of prednisone used to 7.5 mg per day or less. Furthermore, the BLISS-SC study failed to assess the effect of belimumab SC on several other outcome measures considered to be important to patients, including health-related quality of life (HRQoL) and activities of daily living.
3. Patients enrolled in the BLISS-SC study were heterogenous with respect to their standard therapies received at time of enrolment. Furthermore, it is unclear to what extent these treatments were optimized. Therefore, CDEC was unable to identify a subpopulation of patients with SLE who might be more likely to respond to belimumab SC.

Discussion Points

- CDEC discussed that the relapsing, remitting and chronic disabling nature of SLE often results in patients requiring intermittent or continuous use of corticosteroids for flares, but also significantly improving or remitting spontaneously on stable therapy. Patients expressed a desire for treatments that can mitigate the potential adverse effects of long-term corticosteroid use. The duration of BLISS SC was insufficient to determine if belimumab would reduce corticosteroid use in the long-term and/or the adverse effects of cumulative exposure to corticosteroids.
- The duration of the trial was unlikely of sufficient duration to evaluate the effect of preventing long-term organ damage, which was another need identified by patients.
- CDEC noted that the findings of BLISS SC could not be generalized to patients with severe lupus kidney disease, severe active nephritis, or severe central nervous system lupus, who have unmet needs for additional therapies, as these patients were excluded from the trial.
- CDEC discussed the results of the subgroup analyses for the primary outcome and were unable to identify a subgroup based on disease activity or baseline medication use that would benefit from treatment with belimumab.
- CDEC recognizes that SLE is a complex disease with significant needs for patients refractory to current therapies and that individualization of management is a critical component of clinical care. CDEC also noted that the SRI-4 used to define outcomes in the BLISS-SC trial is widely accepted as a useful assessment tool in research, but may not accurately identify all patients who have improved with time.

Background

Belimumab has a Health Canada indication for, in addition to standard therapy for reducing disease activity in adult patients with active, autoantibody-positive, SLE. Belimumab inhibits the B-lymphocyte stimulator and this results in an inhibition of B cell function.

It is available as a 200 mg/mL solution in a single-dose, prefilled syringe or autoinjector for SC injection. The Health Canada–approved dose is 200 mg/mL once weekly.

Submission History

The SC formulation of belimumab has not been previously reviewed by the CADTH Common Drug Review (CDR) for any indication. The intravenous (IV) formulation of belimumab was previously reviewed for the same indication and received a recommendation that belimumab not be reimbursed. (see Notice of CDEC Final Recommendation, April 2012).

Summary of Evidence Considered by CDEC Considerations

CDEC considered the following information prepared by the CADTH CDR: a systematic review of phase III and IV double-blind RCTs of belimumab SC, a summary and critical appraisal of three indirect treatment comparisons (ITCs), and a critique of the manufacturer's pharmacoeconomic evaluation. The committee also considered input from clinical experts with experience in treating patients with SLE, and patient group–submitted information about outcomes and issues important to patients.

Summary of Patient Input

Two patient groups (The Canadian Arthritis Patient Alliance and The Arthritis Society) provided a joint submission for this review. Patient perspectives were obtained from a survey distributed through email and social media. The following is a summary of key input from the perspective of the patient groups:

- Patients described a wide range of symptoms, including swelling, pain, rash, fatigue and cognitive impairment, as well as more serious sequelae such as respiratory and cardiac disorders. The impact on HRQoL is significant, as the various symptoms, most notably pain, fatigue and cognitive impairment, limit their ability to carry out daily activities and work productively.
- Patients noted that many of the treatments currently used to manage the condition (e.g., nonsteroidal anti-inflammatory drugs [NSAIDs], antimalarials, corticosteroids, and immunosuppressives) can be difficult to tolerate and/or can have side effects that require the introduction of even more medications. Patients also commented that responses to the above treatments can vary widely both in terms of effectiveness and durability, and that patients require access to a wide array of treatment options to manage the lifelong condition.
- The key outcomes patients would like to see addressed by a new therapy are pain and fatigue, organ involvement, disease complications, and lupus nephritis. Patients would like new therapies that improve HRQoL through enhanced mobility, productivity and ability to work and carry out activities of daily living and social roles.

Clinical Trials

The systematic review included one phase III, double-blind, placebo-controlled RCT (BLISS-SC, N = 836). Included patients were adults with active SLE who had a SELENA-SLEDAI score of 8 or more. Patients with severe active central nervous system lupus, severe lupus kidney disease (proteinuria > 6 grams/24 hours or equivalent using spot urine protein to creatinine ratio, or serum creatinine > 2.5 mg/dL) or severe active nephritis requiring acute therapy not permitted by protocol or have required hemodialysis or high dose prednisone or equivalent were excluded from the study. Patients were randomized, 2:1, to either belimumab 200 mg (N = 556) or placebo (N = 280) once weekly by SC injection, over a 52 week period. All patients were receiving a background of standard therapy, which could include any of the following alone or in combination: prednisone or equivalent, antimalarials, NSAIDs, or an immunosuppressant.

Key critical appraisal issues included the lack of an active comparator, and the fact that HRQoL, a key outcome from a patient perspective, was not assessed in the double-blind phase of the included study. There was a relatively large number of withdrawals across both groups, and numerically fewer withdrawals in the belimumab group than in the placebo group (17% versus 24% of patients, respectively). The population enrolled into BLISS SC may have represented a population with a more mild form of the disease, as those with more severe forms of SLE (i.e., those with severe renal or central nervous system involvement) were excluded from the trial.

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, CDEC discussed the following: improvement in disease activity (as defined by the composite SRI at 52 weeks, and its individual components), severe flares, reduction in corticosteroid dose, organ damage, and HRQoL. The primary outcome in the included trial was the percent of patients with an SRI response.

- The SRI is a composite that was defined by a ≥ 4 point reduction from baseline in the SELENA-SLEDAI score, no worsening (increase of < 0.30 points from baseline) in the PGA, and no new BILAG A organ domain score or two new BILAG B organ domain scores compared with baseline. The SELENA SLEDAI is a measure of disease activity across nine organ systems, and includes 24 items that assess the following: seizure, psychosis, organic brain syndrome, visual disturbance, cranial nerve disorder, lupus headache, cerebrovascular attack, vasculitis, arthritis, myositis, urinary casts, hematuria, proteinuria, pyuria, rash, alopecia, mucosal ulcers, pleurisy, pericarditis, low complement, increased DNA binding, fever, thrombocytopenia, and leukopenia. On the PGA, physicians are asked to assess their patient's disease activity, between 0 (none) and 3 (severe). The BILAG assesses disease activity across eight organ systems known to be affected by SLE: general, mucocutaneous, neurological, musculoskeletal, cardiorespiratory, vasculitis, renal, and hematologic. The BILAG is an ordinal scale that ranges from A (most active) to E (never present). There is some uncertainty with respect to the cut points to establish clinically meaningful improvement based on the SELENA SLEDAI and PGA, and thus the clinical significance of a patient achieving an SRI response is difficult to ascertain.
- The two secondary outcomes were time to first severe flare over 52 weeks and percent of patients with an average prednisone dose reduction by ≥ 25% from baseline to ≤ 7.5 mg/day during weeks 40 through 52. A severe flare was defined as a change in SELENA SLEDAI score > 12 points, or a new or worse CNS-SLE, vasculitis, nephritis, myositis, platelets < 60 000, hemolytic anemia (hemoglobin < 70 g/L or decrease in hemoglobin > 30 g/L) that requires double prednisone, prednisone increase > 0.5 mg/kg/day, or hospitalization or an increase in prednisone dose to 0.5 mg/kg/day or a new cyclophosphamide, azathioprine, methotrexate, or mycophenolate for SLE, or a hospitalization for SLE, or an increase in PGA score to > 2.5.
- Organ damage was an exploratory outcome and was assessed using the Systemic Lupus International Collaborating Clinics (SLICC)/American College of Rheumatology (ACR) Damage Index (SDI), which consists of 42 items in 12 domains, with a maximum score of 46 (higher scores denote more damage).
- HRQoL, was not investigated in the double-blind phase of BLISS SC, nor was there evidence based on validated scales of the effect of belimumab on symptoms of importance to patients such as pain or cognitive impairment.

Efficacy

More patients in the belimumab than placebo group (61% versus 48%) achieved an SRI response (OR 1.68 [95% CI, 1.25 to 2.25] *P* = 0.0006). The individual components of the SRI were also improved in a greater percent of belimumab patients than placebo: 4-point reduction in SELENA SLEDAI score by week 52 (62% versus 49%, OR of 1.69 [95% CI, 1.26 to 2.27]); no worsening in PGA by week 52 (81% versus 73%, OR of 1.61 [95% CI, 1.15 to 2.27]), and no new 1A/2B BILAG domain scores by week 52 (81% versus 74%, OR of 1.46 [95% CI, 1.04 to 2.07]). There is some uncertainty as to the clinical meaningfulness of the thresholds used for the SELENA SLEDAI and PGA components of the composite primary outcome.

In subgroup analyses for the primary outcome (SRI response), little between-treatment differences were observed in the subgroups of patients not receiving prednisone at baseline, and in the subgroup of patients receiving mycophenolate mofetil at baseline.

There were fewer patients treated with belimumab versus placebo (11% versus 18%) who had a severe flare during the 52-week study (hazard ratio of 0.51 [95% CI, 0.35 to 0.74] *P* = 0.0004). There was no statistically significant difference between belimumab (18% of patients) and placebo (12%) in the percent of patients who were able to reduce their prednisone dose by at least 25%, to 7.5 mg daily or less during weeks 40 through 52 (OR of 1.65 [95% CI, 0.95 to 2.84] *P* = 0.0732). Because patients had to be on a dose of > 7.5 mg prednisone daily at baseline to be included in this analysis, this outcome only included about 60% of the intention-to-treat population. The clinical experts consulted by CDR on this review noted the importance of reducing patients' reliance on corticosteroids, given the severe adverse effects associated with this class of drugs with heavy or prolonged utilization.

The mean difference in the SDI between belimumab and placebo in change from baseline after week 52 was 0.0 (95% CI, –0.1 to 0.00), *P* = 0.1174.

HRQoL was not studied, and symptoms like fatigue were only assessed as exploratory outcomes, a significant limitation of this review, given the importance of these outcomes to patients.

Harms

- Three belimumab patients (0.5% of patients) died (sepsis, urosepsis, and tuberculosis) compared with two patients (0.7% of patients) in the placebo group (thrombocytopenia, cardiac arrest) over the course of the 52-week double-blind treatment phase.
- There were 11% of belimumab patients and 16% of placebo patients who experienced a serious adverse event and 81% of belimumab patients and 84% of placebo patients who had an adverse event.
- There were 7% of patients in the belimumab group and 9% of placebo patients who discontinued the study drug due to an adverse event.
- Among notable harms, post-injection reactions occurred in 7% of belimumab patients and 9% of placebo patients. Psychiatric adverse events occurred in 6% of belimumab and 11% of placebo patients, infections of special interest occurred in 5% of belimumab and 8% of placebo. Tuberculosis occurred in 0.4% of patients in belimumab and 0.7% of patients in placebo, and herpes zoster occurred in 3.1% of belimumab and 4.6% of placebo.

Indirect Treatment Comparisons

Three ITCs were reviewed, one provided by the manufacturer and the other two were published, one by Lee et al. and the other by Tian et al. The manufacturer-provided and Lee et al. analyses compared the efficacy of the two different formulations of belimumab (IV versus SC) with each other, and both included the same studies (BLISS SC for the SC formulation, and BLISS 52 and BLISS 76 for the IV formulation); however, the manufacturer-provided ITC was restricted to patients with high disease activity (HDA), though randomization in the included studies was not stratified by HDA. The ITC by Tian et al. compared safety of all available drugs (immunosuppressive drugs, biologicals, and glucocorticoids) used in the treatment of patients with SLE.

The two ITCs that compared the formulations of belimumab had different findings. The manufacturer-submitted ITC did not favour either the IV or SC formulation of belimumab for SRI response, for patients with a ≥ 4-point reduction in SELENA SLEDAI at week 52, and for severe flares over 52 weeks; while the ITC by Lee et al. found that the IV formulation was favoured over the SC formulation for SRI response at 52 weeks. The ITC by Lee et al. may have reported placebo responses from BLISS 52 incorrectly, and this appears to have been the source of the different responses found between the two formulations. Overall findings from the manufacturer-submitted ITC suggest there is no difference in efficacy between the SC and IV formulations of belimumab in a population of patients with SLE who have HDA.

The published ITC that focused on safety, Tian et al., found no treatment was favoured among belimumab SC and other drugs used for SLE (immunosuppressants, biologics [including the IV formulation of belimumab] and corticosteroids) for mortality, serious adverse events, adverse events, serious infections, and withdrawal due to adverse events. Lee et al. also reported that no treatment was favoured among the two formulations of belimumab and placebo with respect to serious adverse events. Overall findings from ITCs suggest that there are no differences in harms between belimumab SC and other drugs used for SLE.

Cost and Cost-Effectiveness

The submitted price of belimumab is $421.79 per 200 mg pre-filled SC injection. At the recommended dose of 200 mg weekly, the average annual cost is $21,933 per patient.

The manufacturer submitted a cost-utility analysis over a 50-year time horizon. The analysis was conducted from the perspective of a Canadian public health care payer. Primary analysis was conducted for a population based on the BLISS SC trial population: patients with moderate-to-severe SLE (score of ≥ 8 on the SELENA SLEDAI). The analysis considered belimumab in addition to standard of care (SoC) versus SoC alone; where SoC was comprised of corticosteroids, immunosuppressants, antimalarials, and NSAIDs. All components of SoC (excluding NSAIDs) were assumed to vary by comparator.

A Markov model was used to predict the proportion of patients in different states relating to SDI score (0 to 5+) and the presence of cardiovascular (CV) damage. Patients were assumed to only progress (i.e., they could not improve in terms of SDI nor can they recover from CV damage). Patients could transition in terms of disease progression (higher SDI), new CV damage, discontinuation of therapy (for belimumab + SoC only), or die. Transitions for progression of SDI were estimated as follows: For belimumab + SoC responders the probabilities of staying in the current SDI state or progressing by 1 or by 2 points were obtained from one year data from the BLISS SC study for belimumab + SoC patients. For SoC the probabilities of staying in the current SDI state or progressing by 1 or by 2 points were obtained from the BLISS SC study for all patients on placebo + SoC regardless of whether or not they were responders. For belimumab + SoC non-responders the probabilities of staying in the current SDI state or progressing by 1 or by 2 points were assumed to be the same as for all patients on placebo + SoC (including the 49.5% which were responders).Mortality was a function of age specific all-cause mortality, the relative mortality of SLE patients versus the general population, the impact of SLE characteristics on mortality based on Cox regression and some form of calibration. The Cox regression model adopted includes steroid dose, adjusted mean SELENA-SLEDAI (AMS) and SDI as predictors of mortality. For each health state within the model, a range of disease characteristics and treatment uptakes were modelled based on regression equations. Variables tracked were AMS, mean steroid dose (mg/day), mean number of mild/moderate flares, mean number of severe flares, proportion of patients using immunosuppressants, and proportion of patients using antimalarials. For the first year (cycle) of the model, the data for these parameters were obtained from the BLISS SC trial, however belimumab non-responders were not given their actual values but the values for all SoC patients. For subsequent years, an approach similar to that adopted for SDI progression was used in that separate regression equations were estimated for the subgroup on belimumab + SoC patients who were responders and for all patients receiving placebo + SoC. Belimumab + SoC non-responders were again assumed to have the same values as all patients on placebo + SoC (including the 49.5% which were responders). For the all patients with SLE (primary analysis), the manufacturer reported that the incremental cost per quality-adjusted life-year (QALY) gained (ICER) for belimumab + SoC versus SoC alone was $147,695 per QALY, with 0% chance that the ICER was less than $50,000.A Markov model was used to predict the proportion of patients in different states relating to SDI score (0 to 5+) and the presence of

CADTH noted a number of major limitations identified with the manufacturer's analyses:

- The most significant issue was the manufacturer's assumption that a nonresponder receiving belimumab + SoC has the same outcomes as patients receiving SoC. This relates to both SDI transition probabilities and the predictive models relating to AMS, steroid dose, flares, immunosuppressants, and antimalarials. These have direct impact on estimates of costs and QALYs.
- The manufacturer assumed that patients receiving belimumab + SoC could stay on treatment for up to 10 years, but assumed no waning of treatment effect. It was not possible to consider an alternate assumption in the model, as such the implications for this assumption are unknown and biased in favour of belimumab.
- Limitations related to the cost and utility values used in the model were noted.
- The manufacturer assumed that mortality is a function of SDI, AMS, and steroid dose. However, it should be noted that there is no evidence of a direct survival benefit with belimumab + SoC based on the submitted clinical studies and that the evidentiary basis from which to estimate any indirect survival benefit is limited.

Given the above limitations, CADTH conducted a revised analysis to attempt to address the issues identified. It was not possible to reprogram the model to allow probabilistic analysis, so the CADTH revised analysis is based on a deterministic analysis. Also, treatment waning over the 10-year treatment period and the assumed mortality effect could not be addressed through reanalyses.

CADTH estimated a revised ICER of $646,893 for belimumab + SoC compared with SoC alone, for the entire SLE population. A price reduction of 88.3% for belimumab + SoC would be needed to be considered cost-effective at a willingness-to-pay threshold per QALY of $50,000.

November 20, 2019 Meeting (Initial)

CDEC Members

Dr. James Silvius (Chair), Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Mr. Allen Lefebvre, Ms. Heather Neville, Dr. Rakesh Patel, Dr. Danyaal Raza, Dr. Emily Reynen, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

Regrets

None

Conflicts of Interest

None

April 15, 2020 Meeting (Reconsideration)

CDEC Members

Dr. James Silvius (Chair), Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Mr. Allen Lefebvre, Ms. Heather Neville, Dr. Rakesh Patel, Dr. Danyaal Raza, Dr. Emily Reynen, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

Regrets

Two CDEC members did not attend.

Conflicts of Interest

None