CDEC FINAL RECOMMENDATION

BELIMUMAB
(Benlysta – GlaxoSmithKline Inc.)
Indication: Systemic Lupus Erythematosus

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that belimumab not be listed.

Reasons for the Recommendation:
1. In two randomized controlled trials (RCTs) reviewed by CDEC (C1056 and C1057), the proportion of responders was statistically significantly higher for belimumab groups than for placebo at 52 weeks, but not at 76 weeks in the trial that extended beyond one year (C1056). The Committee considered the clinical benefit of belimumab to be uncertain, based on the between-trial variability of results, and the lack of between-treatment differences in outcomes of importance to patients (quality of life and reduction in prednisone dose).
2. Given the uncertain clinical benefit of belimumab, the Committee was unable to adequately assess the cost-effectiveness of belimumab, but considered that the incremental cost per quality-adjusted life-year (QALY) could be higher than the $112,883 reported by the manufacturer.

Of Note:
In assessing the manufacturer's Request for Reconsideration, the Committee considered pooling data from the two phase 3 trials (C1056 and C1057) to be inappropriate. The Committee also noted the absence of benefit in the North American subgroup in study C1056.

Background:
Belimumab has a Health Canada indication for reducing disease activity in adult patients with active, autoantibody-positive systemic lupus erythematosus (SLE) when used in combination with standard therapy.

Belimumab is a fully human monoclonal antibody, classified as an immunosuppressant. It is available as 120 mg and 400 mg vials of lyophilized powder for reconstitution and is administered by intravenous (IV) infusion. The Health Canada–recommended dosage is 10 mg/kg administered every two weeks for the first three doses, and every four weeks thereafter.

Summary of CDEC Considerations:
The Committee considered the following information prepared by the Common Drug Review (CDR): a systematic review of RCTs of belimumab, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group-submitted information about outcomes and issues important to patients.

Clinical Trials
The systematic review included three manufacturer-sponsored double-blind RCTs of adult patients with active autoantibody-positive SLE: one phase 2 dose-ranging trial (study LBSL02) and two phase 3 trials (studies C1056 and C1057). LBSL02 was conducted in North America. Approximately one-half of the patients enrolled in study C1056 were from Canada or the United States, while study C1057 was conducted outside North America. Eligibility for enrolment in all studies was based on the level of disease activity as measured by the Safety of Estrogens in Lupus Erythematosus National Assessment — Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) score.

- LBSL02 (N = 449) included patients with a SELENA-SLEDAI score of 4 or greater. It was a phase 2, 52-week trial that randomized patients to one of three belimumab groups (1 mg/kg, 4 mg/kg, or 10 mg/kg) or placebo given every two weeks for three doses, followed by every four weeks thereafter.
- C1056 (N = 819) and C1057 (N = 865) included patients with a SELENA-SLEDAI score of 6 or greater. They were phase 3, 76-week and 52-week trials, respectively, which randomized patients to one of two belimumab groups (1 mg/kg or 10 mg/kg) or placebo given every two weeks for three doses, followed by every four weeks thereafter.

Patients with severe active lupus nephritis and/or central nervous system lupus were excluded from all trials. Patients in all trials were to maintain stable pre-study regimens of any of the following (alone or in combination): prednisone (up to 40 mg per day), antimalarials, non-steroidal anti-inflammatory drugs (NSAIDs), or immunosuppressive or immunomodulatory agents (except IV cyclophosphamide).

Despite similar inclusion criteria for studies C1056 and C1057, there were notable between-trial differences in patient populations, in terms of: geographic and ethnic origin, duration of disease, and baseline medication use.

The following percentages of patients discontinued belimumab or placebo, respectively, prior to week 52: 19% versus 18% in study LBSL02; 22% versus 26% in study C1056; and 17% versus 21% in study C1057. Discontinuations due to adverse events and lack of efficacy were similar between treatment groups in all studies.

Outcomes
Outcomes were defined a priori in the CDR systematic review protocol. Of these, the Committee discussed the following: treatment response, disease flare, Physician Global Assessment (PGA), change in corticosteroid use, quality of life, mortality, serious adverse events, and adverse events.

The co-primary outcomes in study LBSL02 were change in SELENA-SLEDAI score at week 24 and time to first disease flare.

The primary outcome in studies C1056 and C1057 was the percentage of responders at week 52, based on the SLE Responder Index, which was defined as the percentage of patients who met all three of the following criteria:

- ≥ 4 point reduction from baseline in SELENA-SLEDAI score
- No worsening (increase of < 0.30 points from baseline) in PGA
- No new British Isles Lupus Assessment Group (BILAG) A organ domain score, and no more than one new BILAG B organ domain score, compared with baseline at the time of assessment.

The SELENA-SLEDAI assesses disease activity based on signs and symptoms, laboratory tests, and physician's assessment of nine organ systems. The maximum theoretical score for the SELENA-SLEDAI is 105, with 0 indicating inactive disease. Clinically meaningful differences for the SELENA-SLEDAI are –7 for improvement and +8 for worsening.

The PGA is part of the SELENA-SLEDAI. It is a 0 to 10 cm visual analogue scale. An increase of ≥ 0.3 points is considered clinically significant disease worsening.

The BILAG is an organ-specific physician assessment of eight organ systems: general, mucocutaneous, neurological, musculoskeletal, cardiorespiratory, vasculitis, renal, and hematological. Organ manifestations may be: improved (=1), same (=2), worse (=3), or new (=4) over the last month compared with the previous month. Within each organ system, multiple manifestations and laboratory tests (as applicable) are combined into a single score for that organ. The resulting scores for each organ can be A through E, where A is very active disease, B is moderate activity, C is mild stable disease, D is resolved activity, and E indicates that the organ was never involved.

In all studies, health-related quality of life was assessed using the Medical Outcomes Study Short-Form 36 (SF-36).

Results

Efficacy

The Committee focussed its discussion on results of the Health Canada–approved dose of belimumab from the phase 3 studies. Thus, the results described below are from studies C1056 and C1057, for the belimumab 10 mg/kg and placebo groups only.

- The percentage of responders (based on the SLE Responder Index) was statistically significantly higher for belimumab-treated patients than for placebo at 52 weeks in both studies: 43% versus 34%, and 58% versus 44% for studies C1056 and C1057, respectively. In study C1056, there was no statistically significant between-treatment difference at 76 weeks, or for the pre-specified North American subgroup at 52 weeks.
- A statistically significantly higher percentage of belimumab-treated patients than placebo met all three of the response criteria making up the SLE Responder Index at 52 weeks in study C1057: SELENA-SLEDAI (58% versus 46%), PGA (80% versus 69%), and BILAG (81% versus 73%). In study C1056, statistically significant between-treatment differences were observed in only one of the three SLE Responder Index criteria: SELENA-SLEDAI score at 52 weeks (47% versus 36% of belimumab and placebo-treated patients, respectively).
- The percentage of patients who were able to reduce their average prednisone dose by

≥ 25% from baseline to a dose of ≤ 7.5 mg per day was not statistically significantly different between belimumab and placebo in either study.
- There were no notable differences in quality of life between belimumab and placebo-treated patients, based on the Physical Component Score of the SF-36 in either study.
- The proportion of patients experiencing disease flare was statistically significantly lower for belimumab than for placebo in study C1057, but not in study C1056.
- Trials did not provide evidence that belimumab alters the risk of organ damage.

Harms (Safety and Tolerability)

The Committee discussed harms data from all three trials and all three doses of belimumab.
- The incidence of adverse events, serious adverse events, and death was similar between treatment groups in all trials.
- Numerically more deaths occurred in the belimumab groups (11 deaths) compared with placebo (three deaths). Cause of death in the belimumab groups included infection (n = 3), respiratory failure (n = 3), cardiovascular including stroke (n = 2), cancer (n = 1), suicide (n = 1), and unknown cause (n = 1).
- Compared with placebo, a numerically higher percentage of patients treated with belimumab 10 mg/kg experienced the following serious adverse events: anemia (1% versus 0.1%), depression (0.4% versus 0.1%), pyrexia (1.3% versus 0.4%), infusion-related reaction (0.6% versus 0.3%), and bronchitis (0.4% versus 0.1%).

Cost and Cost-Effectiveness

The manufacturer submitted a cost-utility analysis comparing belimumab plus standard of care (SoC; any of the following: prednisone or equivalent, antimalarials, NSAIDs, or any immunosuppressive therapy) against SoC alone, in a subgroup of patients with SLE enrolled in C1056 and C1057 over a lifetime time horizon (~25 years). The submission relied primarily on data from C1056 and C1057 to estimate the clinical efficacy of belimumab. It was assumed that patients on belimumab without a response at week 52 (defined as a ≥ 4 point reduction from baseline in the SELENA-SLEDAI) discontinued the drug, and patients with a response were treated for a maximum of six years. Regression models were constructed to estimate SELENA-SLEDAI scores after 52 weeks. Data from the Toronto Lupus Cohort were used to provide information on disease activity, organ damage, and steroid use over time, using additional mathematical models.

The manufacturer reported that belimumab plus SoC compared with SoC alone is associated with a cost per QALY of $112,883. Uncertainty regarding the clinical effectiveness affects the certainty that can be placed on the cost-effectiveness estimates. For example, there is no evidence that belimumab alters the risk of organ damage and mortality; the long-term impact of belimumab on disease activity is not clear (no statistical differences in disease activity at 76 weeks between belimumab and SoC), and only a subset of patients from studies C1056 and C1057 were considered. When trying to account for the uncertainty in the clinical evidence, CDR noted that incremental cost per QALY estimates increased above $180,000.

The cost of belimumab is estimated at $1,201 to $1,478 per administration (assuming patient weight of 52 kg to 64 kg); first and subsequent annual costs are approximately $18,018 to $22,176 and $15,616 to $19,219, respectively.

Patient Input Information:
The following is a summary of information provided by three patient groups that responded to the CDR Call for Patient Input.

- Improved quality of life is of key importance for people living with lupus and their caregiving community. The patient groups noted that lupus symptoms decrease quality of life; musculoskeletal pain and fatigue are the most troublesome symptoms for many individuals living with lupus. The nature of the disease (occurrence of unpredictable flares) can make keeping up with job responsibilities a challenge.
- Patients expressed concern that treatment with prednisone can produce serious side effects such as loss of bone density, hypertension, obesity, diabetes, and mood swings. An effective drug that would reduce the need for prednisone is desired by patients.
- Patient group input suggested that belimumab's route of administration (intravenous infusion) is a drawback of therapy; however, patients consider that the inconvenience would be worthwhile if the medication reduced the need for visits to health care providers and improved productivity.

Other Discussion Points:

- The Committee recognized the need for new treatments for SLE, to prevent organ damage and improve quality of life; however, trials provided no evidence that belimumab alters the risk of organ damage or improves quality of life. Further, the Committee noted there was no evidence that belimumab allows patients to reduce prednisone use, an outcome of importance to patients.
- The Committee considered that between-trial differences in patient populations may account for the between-trial variation in results. Thus, the Committee considered pooling of studies C1056 and C1057 to be inappropriate. Further the Committee considered that the reviewed trials may not be generalizable to patients with the greatest therapeutic need, given that patients with severe active lupus involving the kidney or central nervous system were excluded.

CDEC Members:
Dr. Robert Peterson (Chair), Dr. Lindsay Nicolle (Vice-Chair), Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Ms. Cate Dobhran, Mr. Frank Gavin, Dr. John Hawboldt, Dr. Peter Jamieson, Dr. Julia Lowe, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. James Silvius, and Dr. Adil Virani.

February 15, 2012 Meeting

Regrets:
None.

Conflicts of Interest:
None.

April 18, 2012 Meeting

Regrets:
One CDEC member did not attend.

Conflicts of Interest:
None.

About this Document:
CDEC provides formulary listing recommendations to publicly funded drug plans. Both a technical recommendation and plain language version of the recommendation are posted on the CADTH website when available.

CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CDEC made its recommendation. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CDEC deliberations.

The manufacturer has reviewed this document and has not requested the removal of confidential information in conformity with the *CDR Confidentiality Guidelines*.

The Final CDEC Recommendation neither takes the place of a medical professional providing care to a particular patient nor is it intended to replace professional advice.
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