# Belimumab

## Frequently Asked Questions (for prescribers)

BCRenal
Provincial Health Services Authority

### 1. What is belimumab?

Belimumab is B Lymphocyte Stimulator protein (BLyS) specific inhibitor that blocks the binding of soluble BLyS, a B-cell survival factor, to its receptor on B-cells. Belimumab does not bind B-cells directly, but by binding BLyS, belimumab inhibits the survival of B-cells, including autoreactive B-cells, and reduces the differentiation of B-cells into immunoglobulin producing plasma cells.[1]

### 2. What is the evidence supporting the use of belimumab in treating active LN?

The pivotal trial is called BLISS-LN,[2] which is a phase three (3), multinational, multicenter, randomized, double-blind, placebo controlled, 104-week trial conduced at 107 sites in 21 countries. Patients over the age of 18 with biopsy-proven, active lupus nephritis (LN) received belimumab or matching placebo, in addition to standard therapy initiated within 60 days before day one (1) of belimumab.

Active intervention:

- Belimumab intravenous (IV) administration: 10 mg/kg IV every 2 weeks x 3 doses then 10 mg/kg IV every 4 weeks thereafter.

Standard therapy in addition to belimumab or placebo (chosen by investigators):

- Cyclophosphamide 500 mg IV every 2 weeks x 6 doses, followed by azathioprine 2 mg/kg/day PO starting 2 weeks after the last dose of cyclophosphamide.

OR

- Mycophenolate mofetil 3 g/day target, although after 6 months, the dose could be reduced to as low as 1 g/day.

AND

- At the investigator's discretion, methylprednisone 500 mg to 1 g IV could be administered during induction followed by prednisone 0.5 to 1 mg/kg/day PO (total daily dose ≤ 60 mg) tapered over 12 weeks.

Summary of baseline characteristics (N=446):

- Female sex: 88%
- Age: 33.4 ± 10 years
- Race: 50% Asian, 33% White, 14% Black, 2% American Indian or Alaska Native
- Median time from initial diagnosis of systemic lupus erythematosus (SLE) to randomization: 3.3 (0.2 to 8.1) years
- Median time from initial diagnosis of LN to randomization: 0.2 (0.1 to 3.3) years
- Kidney-biopsy LN class:
  - III or IV: 58%
  - III and V or IV and V: 26%
  - V: 16%
- Ratio of urinary protein to creatine: 3.4 ± 3.2
- Estimated glomerular filtration rate (eGFR): 100.5 ± 40.2 mL/min/1.73m$^2$
- SLEDAI-2K score: 12.3 ± 5

The primary end point at week 104 was primary efficacy renal response (PERR): 43% with belimumab vs. 32% with placebo; OR 1.6 (95% CI: 1 to 2.3); p=0.03

- PERR is defined as a ratio of urinary protein to creatinine of ≤ 0.7, which is a reliable

predictor of long-term renal survival. An eGFR that was no worse than 20% below the value before the renal flare (pre-flare value) or eGFR ≥ 60 mL/min/1.73m$^2$, which if below 60 mL/min/1.73m$^2$ is a predictor of poor renal prognosis, and no use of rescue therapy for treatment failure.
    - Patients were considered to have treatment failure if they violated the glucocorticoid rules (taper glucocorticoids to 10 mg or less per day by week 24 and not exceed this dose through week 104 except for short-term rescue treatment for reasons other than LN) or received additional immunosuppressive agents (except topical agents) beyond the induction and maintenance regimens; initiated the use of ACE inhibitors, ARBs, or antimalarial drugs after week 24; or if the standard therapy (cyclophosphamide–azathioprine or mycophenolate mofetil) exceeded permitted doses.
- PERR has prognostic value for long-term renal outcomes of patients with LN.[3,4]

The major secondary end point was a complete renal response (CRR): 30% with belimumab vs. 20% with placebo; OR 1.7 (95% CI: 1.1 to 2.7); p=0.02
- CRR is defined as a ratio of urinary protein to creatinine of <0.5, an eGFR that was no worse than 10% below the pre-flare value or ≥ 90 mL/min/1.73m$^2$, and no use of rescue therapy.

## 3. Is the cost of belimumab covered for my patient?

If your patient meets BC Renal reimbursement criteria for belimumab, is registered in BC Renal's Patient Records and Outcome Management Information System (PROMIS) and is prescribed by a nephrologist associated with a Health Authority Renal Program (HARP), then belimumab is covered.

Applications for coverage are available (at BCRenal.ca) for the following scenarios:

i. Class III or IV with or without class V LN within 4 months of induction treatment and eGFR ≥ 30 mL/min/1.73m$^2$
    - This is the population studied in the BLISS-LN trial, but with the window for reimbursing belimumab extended from 60 to 120 days to allow adequate assessment of the effectiveness of standard therapy before adding belimumab.

ii. Class III or IV LN with or without class V LN within 4 months of induction treatment and eGFR ≤ 30 mL/min/1.73m$^2$
    - This population wasn't studied in the BLISS-LN trial. However, if the patient has a baseline eGFR prior to the onset of LN ≥ 30 mL/min/1.73m$^2$ and now has acute kidney injury with current eGFR ≤ 30 mL/min/1.73m$^2$ or is now on dialysis, then a course of belimumab will be reimbursed in an attempt to reverse kidney function decline, and the need for dialysis.

iii. Resistant class III or IV LN with or without class V LN and eGFR ≥ 30 mL/min/1.73m$^2$
    - This population wasn't studied in the BLISS-LN trial. However, if the patient is resistant to all other induction therapies for LN, including mycophenolate, cyclophosphamide, and mycophenolate with a calcineurin inhibitor (all with corticosteroids), then belimumab will be reimbursed as a last resort therapy.

iv. Pure class V LN
    - This population did not demonstrate

benefit from belimumab in the BLISS-LN trial. However, if the patient is resistant to all other therapies for class V LN including corticosteroids, mycophenolate, calcineurin inhibitors and mycophenolate with calcineurin inhibitors, and has an eGFR ≥ 30 mL/min/1.73m$^2$ and proteinuria ≥ 3.5 g/day, then belimumab will be reimbursed as a last resort therapy.

## 4. How do I obtain approval for belimumab and prescribe it to my patients?

i. Health Authority Renal Program (HARP) associated nephrologist faxes an application to BC Renal.
ii. Applications will be reviewed by two (2) renal pharmacists in consultation with nephrologists if required.
iii. Applicants will receive a written response by fax (approved/denied/need more information).
iv. Applicants who receive an approval letter should submit this, along with a belimumab prescription, to the GlaxoSmithKline (GSK) patient support program (PSP) called Monarch.
v. Funding approval and prescriptions need to completed annually.
vi. The PSP assigns a case manager (registered nurse) who contacts the patient in 48 hours.
vii. The PSP coordinates IV infusions at an infusion center, or teaching and administration of SC injections within 7 days.

## 5. What is the recommended dose of belimumab?

- Intravenous (IV) administration: 10 mg/kg IV every 2 weeks x 3 doses then 10 mg/kg IV every 4 weeks thereafter.[1]
    - Infused over one (1) hour, slow or interrupt if the patient develops an infusion reaction
    - Pre-med with an oral antihistamine, with or without an antipyretic, may be administered before the infusion at the discretion of the physician (e.g., the patient has a history of hypersensitivity to belimumab or is known to have multiple drug allergies) but pre-medications are not universally required.
- Subcutaneous (SC) administration: 400 mg (two 200 mg injections) SC weekly x 4 doses, then 200 mg SC weekly thereafter.[1]
    - Inject into the abdomen or thigh, preferably on the same day each week. When injecting in the same body region, advise the patient to use a different injection site for each injection; never give injections into areas where the skin is tender, bruised, red or hard. When a 400 mg dose is administered at one time, it is recommended that the two (2) individual 200 mg injections be administered at least five (5) cm [approximately two (2) inches] apart
    - Efficacy and safety are based on IV administration and pharmacokinetic modelling simulation.
    - It is recommended the first subcutaneous injection should be under the supervision of a healthcare professional, this will be arranged by the patient support program.
    - If a patient is switching from IV to SC, administer the first SC dose one (1) to two (2) weeks after the last IV dose. The transition can occur any time after the patient completes the first two (2) IV doses.

## 6. What happens if a patient misses a dose?

- If the patient is unable to attend an IV infusion appointment, the missed dose

should be administered as soon as possible.
- If a SC dose is missed, it should be administered as soon as possible. Thereafter, patients can resume dosing on their usual day of administration or start a new weekly schedule from the day that the missed dose was administered.

## 7. Are there any warnings with belimumab use?

These warnings are taken from the belimumab product monograph, and is based on the totality of clinical trials, not just BLISS-LN. Most of the data are from three (3) clinical trials using IV belimumab for the treatment of systemic lupus erythematosus (SLE), in a total of 1,349 patients followed for up to 76 weeks.[1]

- Systemic reactions and hypersensitivity including anaphylaxis.
  - The incidence of all infusion reactions with IV administration may not be different between belimumab and placebo (17% w vs. 15% respectively), and the incidence of all injection related reactions with SC administration is 6.1% vs. 2.5% with placebo.
  - The most common infusion reactions ( ≥ 1% in patients receiving IV) were headache, nausea, arthralgia, hypotension, hypertension and pyrexia. Dermatological reactions (urticaria, other rashes and pruritis) were reported in 1.8% vs. 1.5% with placebo.
  - Injection site reactions include pain, erythema, hematoma, pruritis and induration. Clinically significant hypersensitivity reactions associated with SC administration requiring permanent discontinuation were reported in 0.2% of patients.
  - In clinical trials, serious infusion and hypersensitivity reactions affected less than 1% of patients and occurred more frequently on the day of infusion, and with the first two doses of belimumab. Patients with a history of multiple drug allergies or significant hypersensitivity may be at increased risk.
  - Delay in onset of acute hypersensitivity reactions and recurrence of clinically significant reactions after initial resolution of symptoms following appropriate treatment, have been observed.
  - Patients should be counselled on the signs and symptoms of infusion or injection reactions and the importance of seeking medical attention. For anaphylactic reactions, watch for tachycardia, hypotension, angioedema, and dyspnea. Delayed-type, non-acute hypersensitivity reactions may also occur and include symptoms such as rash, nausea, fatigue, myalgia, headache and facial edema.
  - There is insufficient evidence to determine whether pre-medication diminishes the frequency or severity of infusion reactions.

- Progressive Multifocal Leukoencephalopathy (PML)
  - There are two (2) case reports of PML associated with belimumab published in the literature,[5,6] which caused Health Canada to include PML as a warning in the belimumab product monograph. Although the incidence is unknown, the risk of patients experiencing PML is thought to be extremely low.
  - PML should be considered in any patient treated with belimumab presenting with new onset deficits or deterioration in cognition, speech or ocular functions, and/or motor and gait disturbances, and/or seizures.

- Psychiatric disorders (1.2% vs. 0.4% with placebo):
  - Although it was not found in the BLISS-LN study, depression and suicidality have been reported in other trials with belimumab. In the SLE clinical trials, serious depression was reported in 0.6% vs. 0.3% receiving placebo.
  - Patients should be instructed to contact their healthcare provider in a timely manner if they experience new or worsening depression or suicidal thoughts or behaviour.
  - Clinicians should carefully assess the risk of depression, suicide and self-injury considering the patient's medical history, and current psychiatric status before treatment with belimumab.

## 8. What are common adverse reactions with belimumab?

- Common adverse reactions with belimumab include nausea, diarrhea, pyrexia, nasopharyngitis, bronchitis, insomnia, pain in extremity, depression, migraine/headache, pharyngitis, cystitis, and leukopenia.[1]
- Infections may occur more frequently in patients treated with belimumab vs. placebo (71% vs. 67%). Exercise caution when considering the use of belimumab in patients with severe or chronic infections. Consider interrupting belimumab in patients who develop a new infection while undergoing treatment and monitor these patients closely.[1]
  - The most frequent infections are upper respiratory tract infections, urinary tract infections, nasopharyngitis, sinusitis, bronchitis and influenza.
  - The most serious infections are pneumonia, urinary tract infection, cellulitis and bronchitis.

## 9. Does belimumab interfere with vaccines?

Because of its mechanism of action, belimumab may interfere with the response to immunizations. Limited data suggests that belimumab does not significantly affect the ability to maintain a protective immune response to immunizations received prior to administration of belimumab. Live vaccines should not be given for 30 days before, or concurrently with belimumab as clinical safety has not been studied.[1] Once a patient is receiving belimumab therapy, the best time to administer an inactivated vaccine is unknown. One study protocol administered COVID-19 immunizations at approximately the mid-point between doses of belimumab (e.g., after three days with SC injections and after 14 days with IV infusions), and most patients (90%) exhibited protected levels of SARS CoV-2 IgG after three (3) doses.[7]

## 10. If I prescribe belimumab, what monitoring is required?

In the BLISS-LN study patients were assessed at baseline and then every four (4) weeks. Evaluation included urinalysis, proteinuria, eGFR, use of rescue therapy, adverse weight, vital signs, physical exams and more (see study protocol). Safety assessments included adverse events, infusion reactions, hypersensitivity reactions, infections, depression, and suicide or self injury.[2]

## 11. How long should patients remain on belimumab?

Patients were treated for a total of 2 years in BLISS-LN. BC Renal requires that belimumab treatment be reassessed on at least a once yearly basis. The decision of whether to continue belimumab should be dependent on the patient's clinical status, response to treatment, and history of relapse while off

belimumab. Please refer to the BC Renal belimumab application forms for further guidance.

**12. Is belimumab safe to use during pregnancy?**

No formal studies have been conducted on the use of belimumab in pregnant women. IgG antibodies, including belimumab can cross the placenta. Belimumab should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus. Monitor infants of treated mothers for B-cell reduction and depending upon the results, consider delaying infant vaccination with live viral vaccines.[1]

If prevention of pregnancy is warranted, women of childbearing potential should use adequate contraception while using belimumab and for at least four (4) months after the last belimumab treatment.

**13. Is belimumab safe to use during breastfeeding?**

The safety of belimumab for use during lactation has not been established. There are no data regarding the excretion of belimumab in human milk, or systemic absorption of belimumab after ingestion.[1]

It is recommended that a decision should be made about belimumab therapy in breast-feeding mothers, considering the importance of breast-feeding to the infant and the importance of the drug to the mother, and any potential adverse effects on the breastfed child or from the underlying maternal condition.

**14. Are there any significant drug interactions?**

Formal drug interaction studies have not been performed. In clinical trials, concomitant use of mycophenolate, cyclophosphamide, azathioprine, methotrexate, antimalarials, NSAIDs, aspiring, and HMG-CoA reductase inhibitors did not significantly influence belimumab pharmacokinetics.[1]

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