BELIMUMAB (BENLYSTA – GLAXOSMITHKLINE INC.) FOR SYSTEMIC LUPUS ERYTHEMATOSUS

BACKGROUND

Systemic lupus erythematosus (SLE) is a complex autoimmune disease with heterogeneous clinical manifestations and an unpredictable course of flares and remissions. Females are disproportionately affected (80–90% of cases) and those of black African descent are three times more likely than Caucasians to be affected. Characteristic features of SLE include dysregulated innate and adaptive immune pathways and the development of anti-nuclear autoantibodies. Hyperreactivity of both T and B lymphocytes plays a central role in disease pathogenesis. Hyperreactive B cells lead to autoantibody formation against numerous autoantigens, causing immune complexes to form; these deposit in tissues, resulting in organ damage.

For most individuals, early symptoms of SLE involve the skin and joints, but morbidity and mortality are often due to cardiovascular events and damage to the kidneys. Significant manifestations in the lungs and liver, as well as the gastrointestinal, ophthalmic, hematologic, and central nervous systems, also contribute to the substantial disease burden. Although these agents have been associated with a dramatic improvement in prognosis for patients with SLE over the years, treatment of refractory disease continues to be a therapeutic challenge.

Belimumab is the first biologic agent approved for SLE; it is also the first drug of any kind to be approved for the disease in several decades. Availability on the Canadian market is anticipated in September 2011.

INDICATIONS

Belimumab, in conjunction with standard therapy, is approved for reducing disease activity in adult patients with active, autoantibody-positive SLE. It is notable that the efficacy of belimumab has not been assessed in patients with severe active lupus nephritis, those with severe active central nervous system (CNS) lupus, or in pediatric patients with lupus.

PHARMACOLOGY & PHARMACODYNAMICS

Belimumab is a fully human IgG1 monoclonal antibody that blocks the binding of soluble B-lymphocyte stimulator (BLyS, also referred to as B cell activating factor or BAFF) to its receptors on B cells. BLyS levels are elevated in many patients with SLE and have correlated with disease activity in some studies.

By binding BLyS, belimumab inhibits B cell survival and decreases the differentiation of B cells into immunoglobulin-producing plasma cells. Belimumab also leads to reductions in autoantibodies.

PHARMACOKINETICS

When belimumab is administered intravenously over one hour, maximum serum concentrations are reached shortly after the end of the infusion. In clinical studies, the drug’s volume of distribution of at steady state was 3.7–5.3 L; this is expected to correspond primarily to distribution in plasma and intracellular compartments. While classical biotransformation studies have not been conducted, the expected metabolic pathway for belimumab is degradation to small peptides and individual amino acids by proteolytic enzymes. With recommended dosing, the terminal half-life is approximately 19.4 days.

EFFICACY

Approval of belimumab for SLE was based on positive results from two randomized, double-blinded, placebo-controlled, multicentre, phase III studies – BLISS-52 (52-week follow-up) and BLISS-76 (76-week follow-up). Eligibility criteria for the studies included:

- a diagnosis of SLE according to American College of Rheumatology criteria;
- active disease;
- unequivocally positive antinuclear antibody (titre ≥1:80) or anti-dsDNA antibody (≥30 IU/mL); and
- a stable treatment regimen for at least 30 days before the first dose of study drug.
Notable exclusion criteria for the studies were severe active lupus nephritis or CNS lupus, previous treatment with any B-lymphocyte-targeted drug (including rituximab), and use of intravenous cyclophosphamide within six months of enrollment.\(^7\,9\)

Participants were randomized to receive belimumab 1 mg/kg or 10 mg/kg, or placebo, by intravenous infusion on days 0, 14, and 28, and then every 28 days, in addition to standard of care.\(^9\,10\) The primary efficacy endpoint in both trials was the proportion of responders at week 52 according to the SLE Responder Index (SRI).\(^9\,10\)

At baseline, standard of care medications used in BLISS-52 and BLISS-76, respectively, included corticosteroids (96% and 76%), immunosuppressives (42% and 56%), and antimalarials (67% and 63%).\(^7\,9\,10\)

Overall, the 10 mg/kg dose of belimumab resulted in significantly higher SRI response rates than placebo at week 52 in both pivotal trials; many secondary efficacy endpoints were also improved with belimumab, albeit inconsistently across the trials and belimumab dosages (see Table 1). As noted in the monograph, the reduction in disease activity reflected by SRI responses was related primarily to improvement in mucocutaneous, musculoskeletal, and immunological parameters.\(^7\)

Of note, the beneficial effects of belimumab 10 mg/kg on SRI response rate were no longer statistically significant compared with placebo at the 76-week assessment in BLISS-76 (39% vs. 32%, respectively; p=0.13).\(^12\)

Many disease biomarkers (e.g., anti-dsDNA and complement levels) were significantly improved with belimumab 10 mg/kg in both studies.\(^8\,12\)

**WARNINGS, PRECAUTIONS & ADVERSE EFFECTS**

Notable warnings and precautions for belimumab relate to its potential to cause hypersensitivity and infusion reactions and to its immunomodulatory activity (and resultant risk for development of infections and malignancies). Severe and/or serious infusion or hypersensitivity reactions (e.g., anaphylaxis, bradycardia, hypotension, angioedema, dyspnea) were reported in 1.2% and 0.6% of patients receiving belimumab 10 mg/kg and placebo, respectively, in clinical trials.\(^7\) It is therefore recommended that belimumab be administered under the supervision of a healthcare professional and that resuscitation equipment be readily available.\(^7\)

Serious infections (e.g., pneumonia, urinary tract infection, cellulitis, bronchitis) occurred in 6.0% and 5.2% of patients who received belimumab and placebo, respectively, in clinical trials.\(^7\) Based on potential risk, the manufacturer suggests caution when considering belimumab for patients with chronic infections and recommends against belimumab use in patients receiving therapy for such infections.\(^7\) Malignancies were reported in 0.4% of patients in both belimumab and placebo study cohorts.\(^7\)

Patients should be instructed to contact their healthcare provider if they experience new or worsening depression, suicidal thoughts, or other mood changes, as serious psychiatric events, including serious depression, were reported more frequently with belimumab 10 mg/kg (1.2%) than placebo (0.4%) in controlled studies.\(^7\)

The most commonly reported adverse effects with the recommended dose of belimumab in clinical trials were nausea (15% vs. 12% with placebo), diarrhea (12% vs. 9%), and fever (10% vs. 8%).\(^7\,8\)

The product monograph should be consulted for a more detailed discussion of warnings, precautions, and adverse effects associated with belimumab.

**DRUG INTERACTIONS**

Formal drug interaction studies have not been conducted with belimumab.\(^7\) Based on a lack of clinical data, coadministration with other biologic therapies or intravenous cyclophosphamide is not recommended.\(^7\) As well, live vaccines should not be given for at least 30 days before, or during treatment with, belimumab due to an increased risk of infection.\(^7\,8\)

Limited data suggest that belimumab does not significantly affect the ability to maintain a protective immune response to previously received immunizations (e.g., tetanus, influenza, pneumococcus); however, it may interfere with the response to vaccinations received concurrently.\(^7\,8\)

**DOSAGE, ADMINISTRATION & MONITORING**

Belimumab is administered intravenously over one hour at a dose of 10 mg/kg every 2 weeks for 3 doses, and then every 4 weeks.\(^7\) No maximum duration of treatment has been clearly defined. Infusions can be interrupted, or rates slowed, if patients develop infusion reactions.\(^7\) An oral antihistamine (with or without an antipyretic) may be administered prior to belimumab dosing; however, there is insufficient evidence to determine whether such premedication diminishes the frequency or severity of reactions.\(^7\)

Dosage adjustment does not appear to be necessary for patients with renal or hepatic impairment, and no specific laboratory monitoring is recommended by the manufacturer.\(^7\)

Specialized infusion clinics will be available throughout Canada to facilitate belimumab administration. Clinic details can be obtained by contacting GSK medical information at 1-800-387-7374.\(^7\)

**AVAILABILITY, STORAGE & COST**

Belimumab is supplied as a preservative-free, lyophilized powder to be reconstituted with sterile water for injection and diluted in normal saline prior to administration.\(^7\) The single-use glass vials (120 mg/5 mL vial or 400 mg/20 mL vial) should be stored under refrigeration (2–8°C) in the original carton until use.\(^7\) Reconstituted vials should be refrigerated if not used immediately.\(^7\) Solutions of belimumab diluted in normal saline may be stored under refrigeration or at room temperature; however, the total time from reconstitution to completion of infusion should not exceed eight hours.\(^7\)

The manufacturer’s list price is $277.20 for a 120 mg vial and $924.00 for a 400 mg vial. Based on these prices, the annual cost of the drug to treat a 70 kg patient at the maintenance dose would be about $22,800.

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\(^1\) The SRI is a new composite index that was custom-designed based on negative results from a preliminary study with belimumab.\(^11\) Using SRI criteria, responders were defined as having all of the following at week 52 compared with baseline: (1) a reduction of at least 4 points in the SELENA-SLEDAI score; (2) no new British Isles Lupus Assessment Group (BILAG) A organ domain score and no more than 1 new BILAG B organ domain score; and (3) no worsening (increase <0.3) in Physician’s Global Assessment score.\(^5\,10\)
DISCUSSION

Belimumab is the first drug to be approved for SLE in several decades, and the BLISS studies confirmed its efficacy over placebo in adult patients with active, autoantibody-positive disease. Still, the drug’s beneficial effects have been described as mild or modest,13-15 and several questions remain unanswered regarding optimal use. For example, the role of belimumab in patients with severe active lupus involving the kidneys or CNS—two sites often affected by severe disease—is uncertain, as these populations were excluded from the phase III trials.16 In addition, efficacy in patients of black African heritage has not been clearly established.7 Studies to address these important patient populations, and to evaluate long-term safety and subcutaneous dosing, have either been committed to by the manufacturer or requested of the manufacturer by regulatory agencies, or are underway.11,16,17

Other salient questions relate to appropriate patient selection and duration of treatment. Based on the lack of durability of the primary response in BLISS-76, it has been suggested that there may be a finite duration of drug effectiveness, although a lack of statistical power was also acknowledged as a possible explanation.18 It has also been suggested that belimumab may be less effective in patients with long-standing disease given the numerically superior effects seen in BLISS-52 (mean disease duration, 5.3 years) compared with BLISS-76 (mean disease duration, 7.5 years);17 however, differences between the study populations other than disease duration could account for the results.

Given the available data, it may be prudent to offer patients at least a 12-month trial of belimumab.18 The necessity for protracted courses of therapy should probably be assessed on an individual basis.18

Overall, belimumab represents a welcome step forward in the care of patients with active SLE, although results of future studies are necessary to clearly define its place in therapy.

Table 1 — Selected results from the BLISS-52 and BLISS-76 studies5,10

<table>
<thead>
<tr>
<th>Outcome*</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BLISS-52</td>
</tr>
<tr>
<td></td>
<td>PLA (n=287)</td>
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<tr>
<td>Primary outcome</td>
<td></td>
</tr>
<tr>
<td>SRI response rate</td>
<td>44%</td>
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<tr>
<td>Secondary outcomes</td>
<td></td>
</tr>
<tr>
<td>↓ ≥4 points in SELENA-SLEDAI</td>
<td>46%</td>
</tr>
<tr>
<td>No BILAG worsening</td>
<td>73%</td>
</tr>
<tr>
<td>No PGA worsening</td>
<td>69%</td>
</tr>
<tr>
<td>PGA improvement rate</td>
<td>49%</td>
</tr>
<tr>
<td>Prednisone dose ↓ by ≥25% to ≤7.5 mg/day</td>
<td>12%</td>
</tr>
<tr>
<td>SFI flare rate, severe</td>
<td>23%</td>
</tr>
</tbody>
</table>

BEL = belimumab; BILAG = British Isles Lupus Assessment Group; NR = not reported; PGA = Physician’s Global Assessment; PLA = placebo; SELENA-SLEDAI = Safety of Estrogens in Lupus Erythematosus National Assessment—Systemic Lupus Erythematosus Disease Activity Index; SFI = SLE Flare Index; SRI = SLE Responder Index
* Outcomes were assessed at week 52 (or over 52 weeks) unless otherwise indicated.
† P values reported are for pairwise comparisons with placebo; statistical significance is indicated by values <0.05.
‡ No new BILAG 1A or 2B flares.
§ During weeks 40–52.
5 69% and 46% of patients in BLISS-52 and BLISS-76, respectively, were taking prednisone at doses greater than 7.5 mg/day at baseline.

References
# NEW PRODUCTS/PRODUCT UPDATES

<table>
<thead>
<tr>
<th>TRADE NAME</th>
<th>GENERIC NAME</th>
<th>SOURCE</th>
<th>CLASSIFICATION</th>
<th>SUPPLIED/COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Abilify</strong></td>
<td>Aripiprazole</td>
<td>Bristol Myers Squibb Canada</td>
<td>Antipsychotic</td>
<td><strong>New indication:</strong> As cotherapy with lithium or divalproex sodium for maintaining clinical improvement for up to 1 year in patients with manic or mixed episodes associated with Bipolar I Disorder</td>
</tr>
<tr>
<td><strong>Abstral</strong></td>
<td>Fentanyl</td>
<td>Paladin Labs Inc.</td>
<td>Opioid analgesic</td>
<td>100 µg, 200 µg, 300 µg, 400 µg, 600 µg, and 800 µg sublingual tablets; blister packs of 10</td>
</tr>
<tr>
<td><strong>Biacna Topical Gel</strong></td>
<td>Clindamycin phosphate/tretinoin</td>
<td>Valeant Canada Limited</td>
<td>Antimicrobial and keratolytic (for acne)</td>
<td>1.2%/0.025% w/w gel; tubes of 30 g or 60 g</td>
</tr>
<tr>
<td><strong>Brilinta</strong></td>
<td>Ticagrelor</td>
<td>AstraZeneca Canada Inc.</td>
<td>Platelet aggregation inhibitor</td>
<td>90 mg tablets; packages of 60</td>
</tr>
<tr>
<td><strong>Byetta</strong></td>
<td>Exenatide</td>
<td>Eli Lilly Canada Inc.</td>
<td>Antihyperglycemic agent</td>
<td>250 µg/mL subcutaneous solution in pre-filled pens of 60 doses (5 µg/dose or 10 µg/dose); packages of 1</td>
</tr>
<tr>
<td><strong>Estragyn Vaginal Cream</strong></td>
<td>Estrone</td>
<td>Triton Pharma Inc.</td>
<td>Estrogen</td>
<td><strong>Name change:</strong> Previously Neo-Estrone Vaginal Cream</td>
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<tr>
<td><strong>Gardasil</strong></td>
<td>Human papillomavirus (HPV) vaccine, types 6, 11, 16, and 18</td>
<td>Merck Frosst Canada Ltd.</td>
<td>Active immunizing agent</td>
<td><strong>New/extended indications:</strong> (1) age extension to include females 9–45 years of age; (2) prevention of anal cancer and anal intraepithelial neoplasia (AIN) grades 1, 2, 3</td>
</tr>
<tr>
<td><strong>Moviprep</strong></td>
<td>Polyethylene glycol 3350/sodium sulphate anhydrous/sodium chloride/potassium chloride/ascorbic acid/sodium ascorbate</td>
<td>Medical Futures Inc.</td>
<td>Osmotic laxative (for colonoscopy preparation)</td>
<td>Powder for oral solution; packages of 1 (each package [1 treatment course] contains 2 each of “Sachet A” and “Sachet B”</td>
</tr>
<tr>
<td><strong>Next Choice</strong></td>
<td>Levonorgestrel</td>
<td>Cobalt Pharmaceuticals</td>
<td>Emergency contraception</td>
<td>0.75 mg tablets; packages of 2</td>
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<tr>
<td><strong>Pataday</strong></td>
<td>Olopatadine</td>
<td>Alcon Canada Inc.</td>
<td>Anti-allergy agent</td>
<td>0.2% w/v ophthalmic solution; bottles of 2.5 mL</td>
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<tr>
<td><strong>Tobi Podhaler</strong></td>
<td>Tobramycin</td>
<td>Novartis Pharmaceuticals Canada Inc.</td>
<td>Respiratory antibiotic</td>
<td>28 mg capsules of powder for inhalation; packages of 224 (with Podhaler)</td>
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<tr>
<td><strong>Verdeso</strong></td>
<td>Desonide</td>
<td>GlaxoSmithKline Inc.</td>
<td>Topical corticosteroid therapy</td>
<td>0.05% topical foam; cans of 10 g, 50 g, or 100 g</td>
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<tr>
<td><strong>Vyloma</strong></td>
<td>Imiquimod</td>
<td>Graceway Pharmaceuticals</td>
<td>Immune response modifier</td>
<td>3.75% w/w cream in single-use packets; packages of 28</td>
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<td><strong>Xgeva</strong></td>
<td>Denosumab</td>
<td>Amgen Canada Inc.</td>
<td>Human monoclonal antibody to RANKL; bone metabolism regulator</td>
<td>70 mg/mL subcutaneous solution in single-use vials (120 mg); packages of 1</td>
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<tr>
<td><strong>Zenhale</strong></td>
<td>Mometasone furoate/formoterol fumarate dihydrate</td>
<td>Merck Canada Inc.</td>
<td>Corticosteroid/long-acting beta2-agonist</td>
<td>Metered dose inhalers of 50 µg/5 µg, 100 µg/5 µg, and 200 µg/5 µg per actuation (120 actuations/inhaler); packages of 1</td>
</tr>
</tbody>
</table>

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Drug Information and Research Centre, Ontario Pharmacists’ Association, 375 University Ave., Suite 800, Toronto ON M5G 2J5
Tel: (416) 385-DIRC (3472) 1-800-268-8058 (Ontario only)  Fax: (416) 385-2442  Email: dirc@dirc.ca
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