For ongoing SLE disease activity, it may be time to add BENLYSTA

INDICATION FOR BENLYSTA
BENLYSTA is indicated for the treatment of adult patients with active, autoantibody-positive, systemic lupus erythematosus (SLE) who are receiving standard therapy.

Limitations of Use: The efficacy of BENLYSTA has not been evaluated in patients with severe active lupus nephritis or severe active central nervous system lupus. BENLYSTA has not been studied in combination with other biologics or intravenous cyclophosphamide. Use of BENLYSTA is not recommended in these situations.

How supplied: BENLYSTA (belimumab) for intravenous (IV) use is available as 120 mg in a 5-mL single-dose vial and 400 mg in a 20-mL single-dose vial. BENLYSTA (belimumab) for subcutaneous use (SC) is available as a 200 mg in a 1-mL single-dose prefilled autoinjector and a 200 mg in a 1-mL single-dose prefilled glass syringe.

IMPORTANT SAFETY INFORMATION FOR BENLYSTA
CONTRAINDICATION
Previous anaphylaxis with BENLYSTA.

Please see additional Important Safety Information inside this brochure and full Prescribing Information and Medication Guide for BENLYSTA.
BENLYSTA demonstrated superior efficacy in three Phase III clinical trials

Trials were randomized, double-blind, placebo-controlled, enrolling adults with SLE

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patients enrolled</th>
<th>Treatments</th>
<th>Duration</th>
<th>Regions</th>
</tr>
</thead>
<tbody>
<tr>
<td>BLISS-SC</td>
<td>N=836</td>
<td>BENLYSTA SC 200 mg + standard therapy vs placebo + standard therapy</td>
<td>52 weeks</td>
<td>North America, South America, Europe, and Asia</td>
</tr>
<tr>
<td>BLISS-52</td>
<td>N=865</td>
<td>BENLYSTA IV 1 mg/kg*, BENLYSTA IV 10 mg/kg, or placebo, each in addition to standard therapy</td>
<td>52 weeks</td>
<td>South America, Asia, Eastern Europe, and Australia</td>
</tr>
<tr>
<td>BLISS-76</td>
<td>N=819</td>
<td>BENLYSTA IV 1 mg/kg*, BENLYSTA IV 10 mg/kg, or placebo, each in addition to standard therapy</td>
<td>76 weeks with primary endpoint at 52 weeks</td>
<td>North America and Europe</td>
</tr>
</tbody>
</table>

Phase II clinical trial (N=449)1,5:
- Patients enrolled had SELENA-SLEDAI ≥ 4 and a history of autoantibodies
- BENLYSTA 1, 4, and 10 mg/kg + standard therapy were compared with placebo + standard therapy over 52 weeks
- BENLYSTA did not meet the prespecified co-primary endpoints of percent change in SELENA-SLEDAI at Week 24 and time to first flare over 52 weeks
- 28% of the population was autoantibody-negative at baseline
- Post hoc subgroup analysis showed BENLYSTA may benefit patients who were autoantibody-positive at baseline
This led to the selection of a targeted autoantibody-positive population in the Phase III trials.

IMPORTANT SAFETY INFORMATION FOR BENLYSTA (cont’d)

WARNINGS AND PRECAUTIONS

MORTALITY
In controlled clinical trials, death occurred in 0.8% (11/1,458) of patients treated with BENLYSTA IV and in 0.4% (3/675) of patients receiving placebo. Etiologies included infection, cardiovascular disease, and suicide.
In the controlled trial (N=836), death occurred in 0.5% (3/556) of patients receiving BENLYSTA SC and 0.7% (2/280) of patients receiving placebo. Infection was the most common cause of death.

Phase III trials entry criteria1-4

Patients met the following:
- At least 18 years of age
- A diagnosis of SLE according to the American College of Rheumatology criteria
- Positive antinuclear antibody (ANA) and/or anti-dsDNA test at screening
- Active disease
  - SELENA-SLEDAI score ≥ 8 for BLISS-SC
  - SELENA-SLEDAI score ≥ 6 for BLISS-52 and BLISS-76
- On standard SLE therapy for > 30 days
  - Standard therapy included corticosteroids, immunosuppressive drugs, antimalarials, or nonsteroidal anti-inflammatory drugs (NSAIDs/aspirin, alone or in combination
Patients were excluded if they had1-4:
- Severe active lupus nephritis
- Proteinuria > 6 g over 24 hours or equivalent using spot urine protein to creatinine ratio
- Serum creatinine > 2.5 mg/dL
- Required hemodialysis within 90 days of study entry
- Required high-dose prednisone (> 100 mg/day) within 90 days of study entry
- Severe active CNS lupus
- Patient required therapeutic intervention for any of the following CNS lupus symptoms within 60 days of study entry:
  - Seizures, psychosis, organic brain syndrome, cerebrovascular accident (CVA), cerebritis, or CNS vasculitis
- Use of other biologics or IV cyclophosphamide was not permitted

Multiple disease manifestations were represented in the Phase III trials

Organ involvement at baseline (% of patients)

<table>
<thead>
<tr>
<th>Organ Domain</th>
<th>BLISS-SC (N=836)</th>
<th>BLISS-52 (N=865)</th>
<th>BLISS-76 (N=819)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucocutaneous</td>
<td>88</td>
<td>82</td>
<td>82</td>
</tr>
<tr>
<td>Immunology</td>
<td>76</td>
<td>85</td>
<td>74</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>79</td>
<td>59</td>
<td>73</td>
</tr>
<tr>
<td>Renal</td>
<td>12</td>
<td>20</td>
<td>11</td>
</tr>
<tr>
<td>CV and respiratory</td>
<td>6</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>CNS</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Vascular</td>
<td>8</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Hematological and fever</td>
<td>8</td>
<td>7</td>
<td>12</td>
</tr>
</tbody>
</table>

* Studies were designed to evaluate efficacy in overall disease activity and were not powered to evaluate efficacy in specific organ domains

*The 1-mg/kg dose is not recommended

1 As defined by SELENA-SLEDAI (Safety of Estrogens in Lupus Erythematosus: National Assessment Version of the Systemic Lupus Erythematosus Disease Activity Index)
Clinical trial design (cont’d)

Standard therapy in all treatment arms allowed for NSAID, corticosteroid, antimalarial, and immunosuppressant use alone or in combination.†‡

Standard therapy use at baseline

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Baseline Standard Therapy (% of Patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroids*</td>
<td>0-7.5 mg/day: 26%, &gt;7.5 mg/day: 60%, 0-7.5 mg/day: 27%, &gt;7.5 mg/day: 69%, &gt;7.5 mg/day: 96%</td>
</tr>
<tr>
<td>Antimalarials</td>
<td>0-7.5 mg/day: 30%, &gt;7.5 mg/day: 46%, 0-7.5 mg/day: 46%, &gt;7.5 mg/day: 69%</td>
</tr>
<tr>
<td>Immunosuppressants</td>
<td>0-7.5 mg/day: 42%, &gt;7.5 mg/day: 56%, 0-7.5 mg/day: 46%, &gt;7.5 mg/day: 63%</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>0-7.5 mg/day: 23%, &gt;7.5 mg/day: 41%, 0-7.5 mg/day: 20%, &gt;7.5 mg/day: 56%</td>
</tr>
</tbody>
</table>

IMPORTANT SAFETY INFORMATION FOR BENLYSTA (cont’d)

SERIOUS INFECTIONS

Serious and sometimes fatal infections have been reported in patients receiving immunosuppressive agents, including BENLYSTA. The most frequent serious infections were pneumonia, including bacterial pneumonia, urinary tract infection, cellulitis, herpes zoster, and bronchitis. Use caution in patients with severe or chronic infections. Consider interrupting therapy with BENLYSTA in patients who develop a new infection.

Progressive Multifocal Leuкоencephalopathy (PML): Cases of JC virus-associated PML resulting in neurological deficits, including fatal cases, have been reported in patients with SLE receiving immunosuppressants, including BENLYSTA. If PML is confirmed, consider stopping immunosuppressant therapy, including BENLYSTA.

Permitted changes to standard therapy†‡

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Permitted Changes To Standard Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroids</td>
<td>No maximum dose limitations; can add new</td>
</tr>
<tr>
<td></td>
<td>Maintained within 25% or 5 mg over baseline dose, whichever was higher</td>
</tr>
<tr>
<td></td>
<td>No increases; decreases allowed</td>
</tr>
<tr>
<td>Antimalarials</td>
<td>Dose increases/decreases permitted; can add new</td>
</tr>
<tr>
<td></td>
<td>No further dose increases permitted; decreases allowed. No new medication permitted</td>
</tr>
<tr>
<td>Immunosuppressants</td>
<td>Dose increases/decreases permitted; no new</td>
</tr>
<tr>
<td></td>
<td>No further dose increases permitted; decreases allowed. No new medication permitted</td>
</tr>
</tbody>
</table>

IMPORTANT SAFETY INFORMATION FOR BENLYSTA (cont’d)

HYPERSENSITIVITY REACTIONS (INCLUDING ANAPHYLAXIS) AND INFUSION REACTIONS

Acute hypersensitivity reactions, including anaphylaxis and death, have been reported in association with infusions and injections of BENLYSTA, including in patients who have previously tolerated BENLYSTA. These events generally occurred within hours of the infusion; however, they may occur later. Non-acute hypersensitivity reactions including rash, nausea, fatigue, myalgia, headache, and facial edema, have been reported and typically occurred up to a week following the most recent infusion. Patients with a history of multiple drug allergies or significant hypersensitivity may be at increased risk. Premedication may mitigate or mask an infusion reaction or hypersensitivity response. In the controlled trial of BENLYSTA SC, systemic hypersensitivity reactions were similar to those observed in the IV clinical trials. Anaphylaxis was observed in 0.6% and 0.4% of patients receiving BENLYSTA and placebo, respectively. Manifestations included hypotension, angioedema, urticaria or other rash, pruritus, and dyspnea.

*Budesonide or prednisolone equivalent.
†At Week 24, daily corticosteroid dose (defined as sum of all corticosteroid doses over any 7 consecutive days divided by 7).
‡Within 8 weeks before Week 52, daily corticosteroid dose could not be increased beyond the dose at Week 44 or at baseline, whichever was higher.

Please see additional Important Safety Information on the following pages, and full Prescribing Information and Medication Guide for BENLYSTA.
All 3 components were required at Week 52 for a patient to be considered a responder

- ≥ 4-point reduction in SELENA-SLEDAI score
- Complete elimination of ≥ 1 disease manifestation
- No marked worsening in any organ systems
- No new flare requiring disease-modifying treatment1 (BILAG A), AND
- ≤ 1 flare requiring symptomatic therapy4 (BILAG B)

**SLE Responder Index-4 (SRI-4) composite primary endpoint2-4,7,*†‡§**

**IMPORTANT SAFETY INFORMATION FOR BENLYSTA (cont’d)**

**HYPERSENSITIVITY REACTIONS (INCLUDING ANAPHYLAXIS) AND INFUSION REACTIONS (cont’d)**

Serious infusion reactions (excluding hypersensitivity reactions) were reported in 0.5% and 0.4% of patients receiving BENLYSTA and placebo, respectively and included bradycardia, myalgia, headache, rash, urticaria, and hypotension. BENLYSTA IV should be administered by healthcare providers prepared to manage infusion reactions and anaphylaxis. The infusion rate may be slowed or interrupted if the patient develops an infusion reaction. In the event of a serious reaction, administration of BENLYSTA must be discontinued immediately and appropriate medical therapy administered. Patients should be closely monitored during and for an appropriate period of time after IV administration of BENLYSTA. Patients receiving BENLYSTA should be informed of the signs and symptoms of hypersensitivity reactions and seek immediate medical care should a reaction occur.

**DEPRESSION**

In the controlled clinical trials of BENLYSTA IV, psychiatric events were reported more frequently with BENLYSTA than with placebo, related primarily to depression-related events, insomnia and anxiety. Serious psychiatric events were reported in trials with BENLYSTA. Serious depression and suicidality (including two completed suicides) were reported in trials with BENLYSTA IV. There were no serious depression-related events or suicides reported in the BENLYSTA SC trials. Instruct patients to contact their healthcare provider if they experience new or worsening depression, suicidal thoughts, or other mood changes.

4SRI-4, a primary composite endpoint, comprised of SELENA-SLEDAI, BILAG, and PGA scores.
5SELENA-SLEDAI (Safety of Estrogens in Lupus Erythematosus: National Assessment Version of the Systemic Lupus Erythematosus Disease Activity Index) assesses 24 weighted variables to indicate overall disease severity.
6BILAG (British Isles Lupus Assessment Group) measures flare activity and severity across 8 organ domains.
7PGA (Physician’s Global Assessment) assesses overall severity of SLE disease activity.
8Gluocorticoid > 20 mg/day or immunosuppressants.
9eg, antimalarial drugs, NSAIDs, or glucocorticoids < 20 mg/day.

Please see additional Important Safety Information on the following pages, and full Prescribing Information and Medication Guide for BENLYSTA.
Safety profile of BENLYSTA

Adverse reactions in ≥ 3% of patients receiving BENLYSTA 10 mg/kg + standard therapy and ≥ 1% more frequently than those receiving placebo + standard therapy¹

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>BENLYSTA 10 mg/kg + Standard Therapy (n = 674) %</th>
<th>Placebo + Standard Therapy (n = 675) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>15</td>
<td>12</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>12</td>
<td>9</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>Insomnia</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Depression</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Migraine</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Cystitis</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Gastroenteritis viral</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

The safety profile observed for BENLYSTA administered subcutaneously plus standard therapy was consistent with the known safety profile of BENLYSTA administered intravenously plus standard therapy, with the exception of local injection site reactions.

**IMPORTANT SAFETY INFORMATION FOR BENLYSTA (cont’d)**

**MALIGNANCY**
The impact of treatment with BENLYSTA on the development of malignancies is not known. The mechanism of action of BENLYSTA could increase the risk for the development of malignancies.

**IMMUNIZATION**
Live vaccines should not be given for 30 days before or concurrently with BENLYSTA. BENLYSTA may interfere with the response to immunizations.

**USE WITH BIOLOGIC THERAPIES OR IV CYCLOPHOSPHAMIDE**
BENLYSTA has not been studied in combination with other biologic therapies, including B-cell targeted therapies, or IV cyclophosphamide. Therefore, use of BENLYSTA is not recommended in combination with these therapies.

**ADVERSE REACTIONS**
The most common serious adverse reactions were serious infections (6.0% and 5.2% in patients receiving BENLYSTA IV and placebo, respectively), some of which were fatal. Adverse reactions, regardless of causality, occurring in at least 3% of patients with SLE who received BENLYSTA 10 mg/kg and placebo respectively and, at an incidence at least 1% greater than that observed with placebo in the 3 controlled studies, were: nausea 15% and 12%; diarrhea 12% and 9%; pyrexia 10% and 8%; nasopharyngitis 9% and 7%; bronchitis 9% and 5%; insomnia 7% and 5%; pain in extremity 6% and 4%; depression 5% and 4%; migraine 5% and 4%; pharyngitis 5% and 3%; cystitis 4% and 3%; leukopenia 4% and 2%; viral gastroenteritis 3% and 1%.

The safety profile observed for BENLYSTA SC plus standard therapy was consistent with the known safety profile of BENLYSTA IV plus standard therapy, with the exception of local injection site reactions.

**OTHER IMPORTANT INFORMATION FOR BENLYSTA**

**USE IN SPECIFIC POPULATIONS**

**Pregnancy:** There are insufficient data on use of BENLYSTA in pregnant women to establish whether there is drug-associated risk for major birth defects or miscarriage. Following an assessment of benefit versus risk, if prevention is warranted, women of childbearing potential should use effective contraception during treatment and for at least 4 months after the final treatment.

**Pregnancy Registry:** Healthcare professionals are encouraged to register patients and pregnant women are encouraged to enroll themselves by calling 1-877-681-6296.

**Lactation:** There is no information available on the presence of belimumab in human milk, the effects on the breastfeeding infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for BENLYSTA and any potential adverse effects on the breastfed child from BENLYSTA or from the underlying maternal condition.

**Black/African American Patients:** In clinical studies, there have been mixed results regarding how well BENLYSTA works in black/African American patients. Consider the risks and benefits when prescribing BENLYSTA in black/African American patients.

**References:**

Please see additional Important Safety Information throughout this brochure, and full Prescribing Information and Medication Guide for BENLYSTA.
IMPORTANT SAFETY INFORMATION FOR BENLYSTA (cont’d)

SERIOUS INFECTIONS

Serious and sometimes fatal infections have been reported in patients receiving immunosuppressive agents, including BENLYSTA. The most frequent serious infections were pneumonia, including bacterial pneumonia, urinary tract infection, herpes zoster, and sepsis. Other serious infections reported in clinical trials were gastroenteritis, respiratory tract infections, oral candidiasis, and cellulitis.

PML ( Progressive multifocal leukoencephalopathy)

Confirmed, consider stopping immunosuppressant therapy, including BENLYSTA. Including fatal cases, have been reported in patients with SLE receiving immunosuppressants, including BENLYSTA. If PML is suspected with BENLYSTA in patients who develop a new infection.

CLINICAL TRIAL DESIGN (cont’d)

Standard therapy use at baseline

Standard therapy in all treatment arms allowed for NSAID, corticosteroid, antimalarial, and immunosuppressant use alone or in combination.

BLISS-76 (N=819)

BLISS-52 (N=865)

BLISS-SC (N=836)

1-877-4-BENLYSTA (1-877-423-6597)
Select option 1 for BENLYSTA Gateway Monday-Friday, 8 AM to 8 PM, ET BenlystaHCP.com

REFERENCES:

1.

2.

3.

4.

5.

6.

7.