PDL DRUG REVIEW

Proprietary Name: Benlysta®
Common Name: belimumab
PDL Category: SLE Agents

Summary

Pharmacology/Usage: Belimumab, the active ingredient of Benlysta®, is a human IgG1 lambda monoclonal antibody specific for soluble human B lymphocyte stimulator protein (BLyS). It is a BLyS-specific inhibitor that blocks the binding of soluble BLyS, a B-cell survival factor, to its receptor on B cells. Benlysta® does not bind B cells directly, but by binding BLyS, Benlysta® inhibits the survival of B cells, including autoreactive B cells, and reduces the differentiation of B cells into immunoglobulin-producing plasma cells.

Indications: For the treatment of adults with active, autoantibody-positive, systemic lupus erythematosus (SLE) who are receiving standard therapy. The efficacy of Benlysta® has not been evaluated in patients with severe active lupus nephritis or severe active central nervous system lupus. It has not been studied in combination with other biologics or intravenous cyclophosphamide. Use of Benlysta® is not recommended in these situations.

There is no pregnancy category with this medication; however, the risk summary indicates that the limited available data on use in pregnant women (from observational studies, published case reports, and postmarketing surveillance) are insufficient to inform whether there is a drug-associated risk for major birth defects or miscarriage. There are risks to the mother and fetus associated with SLE. Monoclonal antibodies, such as belimumab, are actively transported across the placenta during the 3rd trimester of pregnancy and may affect immune response in the in utero-exposed infant. Based on animal data and the mechanism of action of belimumab, the immune system in infants of treated mothers may be adversely affected. The safety and efficacy of use in the pediatric population have not been established.

Dosage Forms: Injection for IV infusion: 120mg or 400mg lyophilized powder in single-use vials for reconstitution AND Subcutaneous (SC) injection: 200mg/ml in a single-dose prefilled autoinjector or a single-dose prefilled glass syringe.

Recommended Dosage: *IV infusion regimen:* 10mg/kg at 2-week intervals for the first 3 doses and at 4-weeks interval thereafter. Prior to IV dosing, consider administering premedication for prophylaxis against infusion reactions and hypersensitivity reactions. *SC regimen*: 200mg QW SC in the abdomen or thigh. If transitioning from IV therapy to SC, administer the first SC dose 1 to 4 weeks after the last IV dose.

Dose adjustments are not recommended with renal impairment. While formal studies have not been performed to examine the effects of hepatic impairment, dosage adjustments are not recommended with hepatic impairment.

Drug Interactions: Formal drug interactions have not been performed with Benlysta®.

Live vaccines should not be given for 30 days before or concurrently with Benlysta® as clinical safety has not been established.

Benlysta® has not been studied in combination with other biologic therapies. Use of Benlysta® is not recommended in combination with biologic therapies or IV cyclophosphamide.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Benlysta® + standard therapy) minus reported % incidence for placebo + standard therapy. Please note that an incidence of 0% means the incidence was the same as or that the active drug was less than its comparator.* The most frequently reported adverse events included nausea (3%), diarrhea (3%), pyrexia (2%), nasopharyngitis (2%), bronchitis (4%), insomnia (2%), pain in extremity (2%), depression (1%), migraine (1%), pharyngitis (2%), cystitis (1%), leukopenia (2%), and gastroenteritis viral (2%).In clinical trials with the SC dosage form, the safety profile was consistent with the known safety profile of the IV regimen. Injection site reactions were reported by 6.1% of the Benlysta® SC group as compared with 2.5% of the placebo group.

There were more deaths reported with Benlysta® IV as compared with placebo during clinical trials. Of the 2,133 patients, there were 14 deaths that occurred in the placebo-controlled trials, including 3/675 (0.4%) in the placebo group, 5/673 (0.7%) in the Benlysta® 1mg/kg group, 0/111 (0%) in the Benlysta® 4mg group, and 6/674 (0.9%) in the Benlysta® 10mg group. There was no single cause of death that predominated. In the controlled trial with Benlysta® SC, there were 5 deaths, including 2/280 (0.7%) of the placebo group and 3/556 (0.5%) in the Benlysta® group. Infection was the most common cause of death.

Serious infections and sometimes fatal infections have been reported in patients receiving immunosuppressive agents, including Benlysta®. It is recommended to use caution when considering the use of Benlysta® in those with severe or chronic infections. Consider interrupting therapy with Benlysta® in those who develop a new infection while undergoing treatment with Benlysta®, and monitor them closely. In addition, cases of JC virus-associated progressive multifocal leukoencephalopathy (PML) resulting in neurological deficits, including fatal cases, have been reported in patients with SLE receiving immunosuppressants, including Benlysta®. If confirmed PML, consider stopping immunosuppressant therapy, including Benlysta®.

Psychiatric events were reported more with Benlysta® IV (16%) as compared with placebo (12%), related primarily to depression-related events (6.3% vs 4.7%), insomnia (6% vs 5.3%), and anxiety (3.9% vs 2.8%). Serious psychiatric events were reported in 0.8% in the Benlysta® group vs 0.4% in the placebo group. Psychiatric events were reported in 6% of the Benlysta® SC group vs 11% of the placebo group, with serious psychiatric events reported in 0.2% with Benlysta® vs 0% placebo. Most patients who reported serious depression or suicidal behavior had a history of depression or other serious psychiatric disorders. It is not known if treatment with Benlysta® is associated with increased risk for these events.

The impact of Benlysta® on the development of malignancies is not known. In controlled trials with Benlysta® IV, malignancies were reported in 0.4% of the Benlysta® group vs 0.4% of the placebo group. Data were similar with Benlysta® SC. The mechanism of action of Benlysta® could increase the risk for development of malignancies.

Contraindications: In patients who have had anaphylaxis with belimumab

Manufacturer: Human Genome Sciences, Inc (a subsidiary of GlaxoSmithKline); Marketed by GlaxoSmithKline

Analysis: The safety and efficacy of Benlysta® IV plus standard therapy were assessed in 3 randomized, double-blind, placebo controlled trials (N=2,133) that included adults with SLE. The stable standard therapy was comprised of any of the following, alone or in combination: corticosteroids, antimalarials, NSAIDs, and immunosuppressives. Patients with severe active lupus nephritis and severe active CNS lupus were excluded from the trials.

Study 1 (N=449) included patents randomized to Benlysta® 1mg, 4mg, and 10mg/kg plus standard therapy as compared to placebo plus standard therapy for 52 weeks. All patients had a Safety of Estrogens in Lupus

Erythematosus National Assessment- SLE Disease Activity Index (SELENA-SLEDAI) score of ≥4 at baseline and a history of autoantibodies, but 28% was autoantibody negative at baseline. The co-primary endpoints were the % change in SELENA-SLEDAI score at week 24 and time to first flare over 52 weeks. Significant differences were not seen between any Benlysta® dose and placebo. In an exploratory analysis, a subgroup of patients (72%) who were autoantibody positive appeared to benefit with Benlysta®. Results of this study informed the design of Trials 2 and 3 and led the selection of a target population and indication that is limited to autoantibody-positive SLE patients.

Trials 2 and 3 were both randomized, double-blind, placebo-controlled trials that were similar in design except that trial 2 (N=819) was 76 weeks in duration and trial 3 (N=865) was 52 weeks in duration. At screening, all had active SLE disease with a SELENA-SLEDAI score ≥6 and positive autoantibody test results. In addition, trial 2 was conducted mainly in North America and Europe, while trial 3 was conducted in South America, Eastern Europe, Asia, and Australia. Most patients (≥70%) were receiving ≥2 classes of SLE medication.

The primary endpoint was a composite endpoint (SLE Responder Index-4 or SRI-4) that defined response as meeting each of the following criteria at week 52 compared with baseline: ≥4-point reduction in the SELENA-SLEDAI score, and no new British Isles Lupus Assessment Group (BILAG) A organ domain score or 2 new BILAG B organ domain scores, and no worsening (<0.30-point increase) in Physicians Global Assessment (PGA) score.

In both studies, the proportion with SLE achieving an SRI-4 response, as defined for the primary endpoint, was significantly higher in the Benlysta® 10mg/kg group plus standard therapy as compared with placebo plus standard therapy. The effect on the SRI-4 was not consistently significantly different for patients receiving Benlysta® 1mg/kg plus standard therapy as compared to placebo plus standard therapy in both trials. Thus, the 1mg/kg dose is not recommended. In addition, at week 76 in trial 2, the SRI-4 response rate with Benlysta® 10mg/kg was not significantly different from that of placebo (39% vs 32%, respectively). The table below includes the clinical response rate in patients after 52 weeks of treatment from trials 2 and 3, which was adapted from the prescribing information.

	Trial 2			Trial 3		
Response	Placebo (N=275)	Benlysta® 1mg/kg (N=271)	Benlysta® 10mg/kg (N=273)	Placebo (N=287)	Benlysta® 1mg/kg (N=288)	Benlysta® 10mg/kg (N=290)
SRI-4	34%	41%	43%	44%	51%	58%
Odds Ratio, p-value	-	1.3; p=0.104	1.5; P=0.021	-	1.6; p=0.013	1.8; p<0.001
Components of SRI-4						
% with reduction in SELENA-SLEDAI≥4	36%	43%	47%	46%	53%	58%
% with no worsening by BILAG index	65%	75%	69%	73%	79%	81%
% with no worsening by PGA	63%	73%	69%	69%	79%	80%

Exploratory sub-group analyses of SRI-4 response rates were performed in black patients (N=148). The SRI-4 response rate in black patients receiving Benlysta® plus standard therapy was less than when receiving placebo plus standard therapy (44% placebo vs 31% Benlysta® 1mg/kg and 36% Benlysta® 10mg/kg). While no definitive conclusion can be drawn, caution should be used when considering treatment with Benlysta® in black/African-American patients.

In trials 2 and 3, 46% and 69% of patients, respectively, were receiving prednisone at doses >7.5mg/day at baseline. The proportion able to reduce their average prednisone dose by at least 25% to ≤7.5mg/day during weeks 40 through 52 were not consistently significantly different for Benlysta® relative to placebo. In trial 2, 17% of the Benlysta® 10mg/kg group and 19% of the Benlysta® 1mg/kg group achieved this level of steroid reduction compared with 13% of the placebo group. In trial 3, 19%, 21%, and 12% receiving Benlysta® 10mg/kg, Benlysta® 1mg/kg, and placebo, respectively, achieved this level of steroid reduction.

The probability of experiencing a severe SLE flare was calculated for trials 2 and 3. The proportion having at least 1 severe flare over 52 weeks was not consistently significantly different for Benlysta® vs placebo in both trials. In trial 2, 18% of the Benlysta® 10mg/kg group and 16% of the Benlysta® 1mg/kg group had a severe flare compared with 24% of placebo. In trial 3, 14%, 18%, and 23%, respectively, had a severe flare.

The safety and efficacy of Benlysta® SC were assessed in a randomized, double-blind, placebo-controlled study (N=836) that included adults with SLE who had a SELENA-SLEDAI score ≥8 and positive autoantibody test results at screening. More than 50% had 3 or more active organ systems involved at baseline. The primary endpoint was the SLE Responder Index-4 (SRI-4) at week 52, as described in the IV trials. Results suggested that the proportion achieving an SRI-4 response was significantly higher with Benlysta® plus standard therapy as compared with placebo plus standard therapy. Results can be seen in the table below, which was adapted from the prescribing information.

Response	Placebo (N=279)	Benlysta® (N=554)
SLE Responder Index-4 (SRI-4)	48%	61%
Odds Ratio, p-value	-	1.7; p=0.0006
Components of SLE-Responder Index-4 (SRI-4)		
% with reduction in SELENA-SLEDAI ≥4	49%	62%
% with no worsening by BILAG index	74%	81%
% with no worsening by PGA	73%	81%

Exploratory sub-group analyses of SRI-4 response rate in black patients (N=91) were performed. The SRI-4 response rate was slightly higher in black patients receiving Benlysta® vs placebo (45% vs 39%), but the treatment difference was not as large as that seen in the overall population and no definitive conclusion can be drawn from this subgroup analysis. It is recommended to use caution when considering treatment with Benlysta® in black/African-American patients.

At baseline, at least 60% were receiving prednisone doses at >7.5mg/day. Of these, 18% receiving Benlysta® reduced the average prednisone dose by at least 25% to ≤7.5mg/day during weeks 40 through52 as compared with 12% of placebo. This difference, however, was not statistically significant (OR 1.65).

The probability of experiencing a severe SLE flare was also calculated in this study. The proportion reporting at least 1 severe flare during the study was lower with Benlysta® compared with placebo (11% vs 18%). The Benlysta® group had a 49% lower risk of experiencing at least 1 severe flare during the 52 weeks of observation, relative to the placebo group (HR 0.51). Of those experiencing a severe flare, the median time to the first severe flare was delayed with the Benlysta® group vs placebo (171 days vs 118 days).

Place in Therapy: Benlysta® is indicated for the treatment of adults with active, autoantibody-positive, systemic lupus erythematosus (SLE) who are receiving standard therapy. The efficacy of Benlysta® has not been evaluated in patients with severe active lupus nephritis or severe active central nervous system lupus. It has not been studied

in combination with other biologics or intravenous cyclophosphamide. Use of Benlysta® is not recommended in these situations. Sub-group analyses of clinical trials determined that caution should be used when considering treatment in black/African-Americans as the SRI-4 response was less in the Benlysta® IV group than placebo. In the SC studies the SRI-4 response rate was higher in the black population as compared with placebo, but no definitive conclusion could be drawn. It is still, however, recommended to use caution when considering treatment with Benlysta® SC in black/African-American patients.

It is recommended that Benlysta® SC injection be added to the PDL as non-preferred and require clinical prior authorization to be able to verify diagnosis and prior trials of preferred more cost-effective medications.

PDL Placement: ☐ **Preferred**
☒ **Non-Preferred**

References

[1] Benlysta [package insert]. Rockville, MD; Human Genome Sciences, Inc (a subsidiary of GlaxoSmithKline) AND research Triangle Park; GlaxoSmithKline; 2017.