BENLYSTA®

PRODUCT INFORMATION

NAME OF THE MEDICINE

The active ingredient of BENLYSTA® is belimumab (rmc).

DESCRIPTION

Belimumab is a fully human IgG1λ monoclonal antibody specific for soluble human B Lymphocyte Stimulator protein (BLyS). It has a molecular weight of approximately 147 kDa.

Belimumab is produced by recombinant DNA technology in a mammalian cell expression system.

CAS number: 356547-88-1

BENLYSTA is a sterile, white to off-white lyophilized powder in a single-use vial.

Each vial contains a sufficient amount of belimumab to deliver 120 mg in 1.5 mL or 400 mg in 5 mL when reconstituted as recommended with sterile Water for Injections. After reconstitution, each mL of solution contains 80 mg belimumab with a pH of 6.5. BENLYSTA also contains sodium citrate, citric acid- monohydrate, sucrose and polysorbate 80.

PHARMACOLOGY

Mechanism of Action

B-Lymphocyte Stimulator (BLyS, also referred to as BAFF and TNFSF13), a member of the tumour necrosis factor (TNF) ligand family, inhibits B-cell apoptosis and stimulates the differentiation of B cells into immunoglobulin-producing plasma cells. BLyS is overexpressed in patients with SLE. There is a strong association between SLE disease activity (as assessed by the Safety of Estrogen in Lupus Erythematosus National Assessment-Systemic Lupus Erythematosus Disease Activity Index [SELENA-SLEDAI]) and plasma BLyS levels.

Belimumab is a fully human IgG1λ monoclonal antibody that specifically binds to soluble human BLyS and inhibits its biological activity. 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.

Pharmacodynamic Effects

Reductions in elevated levels of serum IgG and in anti-dsDNA antibodies were observed as early as Week 8 and continued to Week 52. In patients with hypergammaglobulinemia at baseline, normalization of IgG levels was observed by week 52 in 49% and 20% of patients receiving belimumab and placebo, respectively. In patients with anti-dsDNA antibodies at baseline, reductions in patients receiving belimumab were evident as early as Week 8, and by Week 52, 16% of patients treated with belimumab had converted to anti-dsDNA negative compared with 7% of the patients receiving placebo.

In patients with low complement levels at baseline, belimumab treatment resulted in increases in complement which were seen as early as Week 4 and continued over time. By Week 52, levels of C3 and C4 had normalized in 38% and 44% of patients receiving belimumab compared with 17% and 19% of patients receiving placebo.

The target of belimumab, BLyS, is a critical cytokine for B-cell survival, differentiation, and proliferation. Belimumab significantly reduced circulating B cells, naïve, activated, plasma, and the SLE B cell subset at Week 52. Reductions in naïve, plasma and short-lived plasma cells as well as the SLE B cell subset were observed as early as Week 8. Memory cells increased initially and slowly declined toward baseline levels by Week 52.

Immunogenicity

In the two Phase III studies, 4 out of 563 (0.7%) patients in the 10 mg/kg group and 27 out of 559 (4.8%) patients in the 1 mg/kg group developed persistent anti-belimumab antibodies. The reported frequency for the 10 mg/kg group may underestimate the actual frequency due to lower assay sensitivity in the presence of high drug concentrations.

Neutralising antibodies were detected in 3 patients receiving belimumab 1 mg/kg. However, the presence of anti-belimumab antibodies was relatively uncommon and no definitive conclusions can be drawn regarding the effect of immunogenicity on belimumab pharmacokinetics due to low numbers of anti-belimumab antibody positive subjects.

Pharmacokinetics

The pharmacokinetic parameters below are based on population pharmacokinetic analysis using data from SLE patients who received single or multiple IV infusions of belimumab. The pharmacokinetic parameters reported are the geometric means (5^{th} percentile – 95^{th} percentile) of the individual pharmacokinetic parameter estimates of the 563 patients who received belimumab 10 mg/kg in the two Phase III studies.

Absorption

Belimumab is administered by intravenous infusion. Maximum serum concentrations of belimumab were generally observed at, or shortly after, the end of the infusion. The maximum serum concentration was 311 (231–448) µg/mL based on simulating the

concentration time profile using the typical parameter values of the population pharmacokinetic model.

Distribution

Belimumab distributed to tissues with an overall volume of distribution of 5.22 (4.31–6.41) L.

Metabolism

Belimumab is a protein for which the expected metabolic pathway is degradation to small peptides and individual amino acids by widely distributed proteolytic enzymes. Classical biotransformation studies have not been conducted.

Elimination

Serum belimumab concentrations declined in a bi-exponential manner, with a distribution half-life of 1.68 (1.35–2.09) days and terminal half-life 18.0 (11.6–28.0) days. The systemic clearance was 232 (134–397) mL/day.

Special Patient Groups

The following information is based on the population pharmacokinetic analysis.

Elderly

Belimumab has been studied in a limited number of elderly patients. Within the overall SLE IV study population, age did not affect belimumab exposure in the population pharmacokinetic analysis. However, given the small number of subjects 65 years or older (less than 1.6% of the studies population), an effect of age cannot be ruled out conclusively and belimumab should be administered with caution in this age group.

Children and adolescents

No pharmacokinetic data are available in paediatric patients.

Renal impairment

No formal studies were conducted to examine the effects of renal impairment on the pharmacokinetics of belimumab. During clinical development, belimumab was studied in a limited number of SLE patients with renal impairment (creatinine clearance <60 mL/min, including a small number with creatinine clearance <30 mL/min). Although proteinuria ($\geq$ 2 g/day) increased belimumab clearance, and decreases in creatinine clearance decreased belimumab clearance, these effects were within the expected range of variability. Therefore, no dose adjustment is recommended for patients with renal impairment.

Hepatic impairment

No formal studies were conducted to examine the effects of hepatic impairment on the pharmacokinetics of belimumab. IgG1 molecules such as belimumab are catabolised by widely distributed proteolytic enzymes, which are not restricted to hepatic tissue; therefore, changes in hepatic function are unlikely to have any effect on the elimination of belimumab.

Other patient characteristics

There was no significant effect of gender, race or ethnicity on the pharmacokinetics of belimumab. The effects of body size on belimumab exposure are accounted for by weight normalized dosing.

CLINICAL TRIALS

Phase II Study

The efficacy of belimumab in the treatment of SLE was evaluated in a randomised, placebo-controlled Phase II study in patients with a SELENA SLEDAI score of >4 at baseline and a history of autoantibodies (patients were not required to be autoantibody-positive - 28% of the population was autoantibody negative at baseline). Patients with severe active lupus nephritis and severe active CNS lupus were excluded. Patients were receiving a stable standard of care SLE treatment regimen comprising any of the following (alone or in combination): corticosteroids, antimalarials, NSAIDs, and immunosuppressives. These medications could be changed during the study as clinically indicated. Other biological agents and intravenous cyclophosphamide were not permitted. This study enrolled 449 patients and evaluated doses of 1, 4, and 10 mg/kg belimumab plus standard of care compared with placebo plus standard of care. The co-primary endpoints of this study, percent change in SELENA SLEDAI score at Week 24 and time to first mild, moderate or severe flare over 52 weeks, were not met. However, post-hoc analysis identified a large subgroup of patients (72%), who were autoantibody positive (ANA or anti-dsDNA), in whom belimumab appeared to offer benefit. The results of this study informed the design of the Phase 3 program including the patient population, dose selection and concomitant medication controls.

Phase III Studies

The efficacy of BENLYSTA was evaluated in two randomised, double-blind, placebo-controlled Phase III studies in 1,684 patients with a clinical diagnosis of SLE according to the American College of Rheumatology classification criteria. Eligible patients had active SLE disease, defined as a SELENA-SLEDAI score ≥6 and positive anti-nuclear antibody (ANA or anti-dsDNA) test results (ANA titre ≥1:80 and/or a positive anti-dsDNA [≥30 units/mL]) at screening. Patients were on a stable SLE treatment regimen (standard of care) consisting of any of the following (alone or in combination): corticosteroids, anti-malarials, NSAIDs or other immunosuppressives. Patients were excluded from the study if they had severe active central nervous system lupus or severe active lupus nephritis, had ever received treatment with any B-cell targeted therapy, if they had received another biological investigational agent in the previous year, or if they had a positive response to testing for HIV antibody, hepatitis B surface antigen, or hepatitis C

antibody. The two studies were similar in design except that BLISS-76 was a 76-week study and BLISS-52 was a 52-week study. Both studies had 52 week primary endpoints.

BLISS-76 (HGS1006-C1057) was conducted primarily in North America and Western Europe. The racial distribution was 70% white/Caucasian, 14% black/African American, 13% Alaska native or American Indian, and 3% Asian. Background medications included corticosteroids (76%), immunosuppressives (56%), and anti-malarials (63%).

BLISS-52 (HGS1006-C1056) was conducted in South America, Eastern Europe, Asia, and Australia. The racial distribution was 38% Asian, 26% white/Caucasian, 32% Alaska native or American Indian, and 4% black/African American. Background medications included corticosteroids (96%), immunosuppressives (42%), and anti-malarials (67%).

Patient median age across both studies was 37 years (range: 18 to 73 years), and the majority (94%) were female. At screening, patients were stratified by disease severity based on their SELENA-SLEDAI score ($\leq$ 9 vs $\geq$10), proteinuria level (<2 g per 24 hr vs $\geq$2 g per 24 hr), and race, and then randomly assigned to receive BENLYSTA 1 mg/kg, BENLYSTA 10 mg/kg, or placebo in addition to standard of care. The patients were administered study medication intravenously over a 1-hour period on Days 0, 14, 28, and then every 28 days for 48 or 72 weeks.

The primary efficacy endpoint was a composite endpoint (SLE Responder Index) that defined response as meeting each of the following criteria at Week 52 compared with baseline:

- $\geq$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 Physician's Global Assessment score (PGA),

The SLE Responder Index uses the SELENA-SLEDAI score as an objective measure of reduction in global disease activity; the BILAG index to ensure no significant worsening in any specific organ system; and the PGA to ensure that improvements in disease activity are not achieved at the expense of the patient's overall condition.

BENLYSTA produced significant improvements in the SLE Responder Index as well as in the individual component SELENA-SLEDAI score in both studies, see Table 1.

Table 1: Response Rate at Week 52

	BLISS-76			BLISS-52			BLISS-76 and BLISS-52 Pooled	
		BENLYSTA (mg/kg|)			BENLYSTA (mg/kg)			BENLYSTA (mg/kg)
Response	Placebo (n=275)	1* (n=271)	10 (n=273)	Placebo (n=287)	1* (n=288)	10 (n=290)	Placebo (n=562)	10 (n=563)
SLE Responder Index	33.8%	40.6% p=0.104	43.2% p=0.021	43.6%	51.4% p=0.013	57.6% p=0.0006	38.8%	50.6% p<0.0001
		Components of SLE Responder Index						
Percent of patients with reduction in SELENA-SLEDAI ≥4	35.6%	42.8%	46.9% p=0.006	46.0%	53.1%	58.3% p=0.0024	40.9%	52.8% p<0.0001
Percent of patients with no worsening by BILAG index	65.1%	74.9%	69.2% p=0.32	73.2%	78.9%	81.4% p=0.018	69.2%	75.5% p=0.019
Percent of patients with no worsening by PGA	62.9%	72.7%	69.2% p=0.13	69.3%	78.8%	79.7% p=0.0048	66.2%	74.6% p=0.0017

*The 1 mg/kg dose is not recommended

In a pooled analysis of the two studies, the percentage of patients receiving >7.5 mg/day prednisone (or equivalent) at baseline whose average corticosteroid dose was reduced by at least 25% from baseline to a dose equivalent to prednisone ≤ 7.5 mg/day during Weeks 40 through 52, was 17.9% (58/324) in the group receiving BENLYSTA and 12.3% (39/318) in the group receiving placebo (P=0.0451).

Flares in SLE were defined by the Modified SELENA SLEDAI SLE Flare Index where the modification excludes severe flares that are triggered only by an increase of SELENA SLEDAI score to > 12. The median time to the first flare was delayed in the pooled group receiving BENLYSTA compared to the group receiving placebo (hazard ratio= 0.84, 95% CI (0.74,0.96), P=0.012). The risk of severe flares was also reduced by 36% over the 52 weeks of observation in the group receiving BENLYSTA relative to the group receiving placebo (hazard ratio=0.64, 95% CI (0.49,0.84) P=0.0011).

There were too few males, patients over 65 years of age, or black/African American patients enrolled in the controlled clinical trials to draw meaningful conclusions about the effects of gender, age, or race on clinical outcomes.

At Week 76 in Study 2, the SRI response rate with belimumab was not significantly different from that of placebo (39% and 32% respectively).

Post-hoc analysis has identified high responding subgroups such as those patients with low complement and positive anti-dsDNA at baseline, see Table 2.

Table 2: Patients with low complement and positive anti-dsDNA at baseline

Subgroup	Anti-dsDNA positive AND low complement	
BLISS-76 and BLISS-52 pooled data	Placebo (n=287)	Benlysta 10 mg/kg (n=305)
SRI response rate at Week 52 (%) Observed treatment difference vs placebo (%)	31.7	51.5 (p<0.0001) 19.8
SRI response rate (excluding complement and anti-dsDNA changes) at Week 52 (%) Observed treatment difference vs placebo (%)	28.9	46.2 (p<0.0001) 17.3
Severe flares over 52 weeks Patients experiencing a severe flare (%) Observed treatment difference vs placebo (%) Time to severe flare [Hazard ratio (95% CI)]	29.6	19.0 10.6 0.61 (0.44, 0.85) (p=0.0038)
Prednisone reduction by ≥25% from baseline to ≤7.5 mg/day during Weeks 40 through 52* (%) Observed treatment difference vs placebo (%)	(n=173) 12.1	(n=195) 18.5 (p=0.0964) 6.3
FACIT-fatigue score improvement from baseline at Week-52 (mean) Observed treatment difference vs placebo (mean difference)	1.99	4.21 (p=0.0048) 2.21
BLISS-76 Study only	Placebo (n=131)	Benlysta 10 mg/kg (n=134)
SRI response rate at Week-76 (%) Observed treatment difference vs placebo (%)	27.5	39.6 (p=0.0160) 12.1

* Among patients with baseline prednisone dose >7.5 mg/day

INDICATIONS

BENLYSTA is indicated as add-on therapy for reducing disease activity in adult patients with active, autoantibody-positive systemic lupus erythematosus (SLE) with a high degree of disease activity (e.g. ANA titre ≥ 1:80 and/or anti-dsDNA titre ≥30 IU/mL) despite standard therapy.

The safety and efficacy of BENLYSTA have not been evaluated in patients with severe active lupus nephritis or severe active central nervous system lupus.

CONTRAINDICATIONS

BENLYSTA is contraindicated in patients who have demonstrated anaphylaxis to belimumab or to any of the excipients (See *DESCRIPTION*).

PRECAUTIONS

BENLYSTA has not been studied in the following patient groups:

- severe active central nervous system lupus
- severe active lupus nephritis.
- HIV
- a history of, or current, hepatitis B or C
- hypogammaglobulinaemia (IgG <400 mg/dl) or IgA deficiency (IgA <10 mg/dl)
- a history of major organ transplant or hematopoietic stem /cell /marrow transplant or renal transplant.

Concomitant use with B-cell targeted therapy

BENLYSTA has not been studied in combination with other B-cell targeted therapy or intravenous cyclophosphamide.

Infusion reactions and hypersensitivity

As with all protein products, administration of BENLYSTA may result in hypersensitivity reactions and infusion reactions, which can be severe, and can be fatal. In the event of a severe reaction, BENLYSTA administration must be interrupted and appropriate medical therapy administered (see section *DOSAGE AND ADMINISTRATION*). Patients with a history of multiple drug allergies or significant hypersensitivity may be at increased risk (see *ADVERSE EFFECTS*).

In clinical trials, serious infusion and hypersensitivity reactions affected less than 1% of patients, and included anaphylactic reaction, bradycardia, hypotension, angioedema, and dyspnea. Infusion reactions occurred more frequently with the first two infusion days and tended to decrease with subsequent infusions. Delay in the onset of acute hypersensitivity reactions has been observed. Therefore, patients should be monitored during and for an

appropriate period of time after administration of BENLYSTA. Patients treated with belimumab should be made aware of the potential risk, the signs and symptoms of such reactions, and the importance of immediately seeking medical attention.

Infections

As with other immunomodulating agents, the mechanism of action of BENLYSTA may increase the potential risk for the development of infections. Patients who develop an infection while undergoing treatment with BENLYSTA should be monitored closely. Physicians should exercise caution when considering the use of BENLYSTA in patients with chronic infections. Patients receiving any therapy for chronic infection should not begin therapy with BENLYSTA.

Immunisation

Live vaccines should not be given concurrently with BENLYSTA as clinical safety has not been established. No data are available on the secondary transmission of infection from persons receiving live vaccines to patients receiving BENLYSTA. Because of its mechanism of action, BENLYSTA may interfere with the response to immunisations. The efficacy of concurrent vaccination in patients receiving BENLYSTA is not known. Limited data suggest that BENLYSTA does not significantly affect the ability to maintain a protective immune response to immunisations received prior to administration of BENLYSTA.

Risk of malignancies

As with other immunomodulating agents, the mechanism of action of BENLYSTA may increase the potential for the development of malignancies. Caution should be exercised when considering belimumab therapy for patients with a history of malignancy or when considering continuing treatment in patients who develop malignancy. In clinical trials, there was no difference in the rate of malignancies between BENLYSTA-treated and placebo-treated groups. In the controlled clinical trials, malignancies (including non-melanoma skin cancers) were reported in 0.4% of patients receiving BENLYSTA and 0.4% of patients receiving placebo. In the controlled clinical trials, malignancies, excluding non-melanoma skin cancers, were observed in 0.2% (3/1458) and 0.3% (2/675) of patients receiving BENLYSTA and placebo, respectively.

Depression

Depression and suicidality have been reported in BENLYSTA studies. Patients should be instructed to contact their healthcare provider if they experience new or worsening depression, suicidal thoughts or other mood changes.

Mortality

There were more deaths reported with BENLYSTA than with placebo during the controlled period of the clinical trials. Out of 2133 patients in 3 clinical trials, a total of 14 deaths

occurred during the placebo-controlled, double-blind treatment periods: 3/675 (0.4%), 5/673 (0.7%), 0/111 (0%), and 6/674 (0.9%) deaths in the placebo, BENLYSTA 1 mg/kg, BENLYSTA 4 mg/kg, and BENLYSTA 10 mg/kg groups, respectively. No single cause of death predominated. Etiologies included infection, cardiovascular disease and suicide. The physicians should discuss this imbalance with their patients prior to initiating therapy.

Effects on Fertility:

There are no data on the effects of BENLYSTA on human fertility. Effects on male and female fertility have not been evaluated in animal studies.

Use in Pregnancy (Category C):

There are a limited amount of data from the use of BENLYSTA in pregnant women. Reproductive studies have been performed in pregnant cynomolgus monkeys receiving belimumab 150 mg/kg by intravenous infusion (approximately 9 times the anticipated maximum human clinical exposure) every 2 weeks for up to 21 weeks, and BENLYSTA treatment was not associated with direct or indirect harmful effects with respect to maternal toxicity, developmental toxicity, or teratogenicity. Treatment-related findings were limited to the expected reversible reduction of B cells in both dams and infants and reversible reduction of IgM in infant monkeys. B cell numbers recovered after the cessation of belimumab treatment by about 1 year post-partum in adult monkeys and by 3 months of life in infant monkeys; IgM levels in infants exposed to belimumab in utero recovered by 6 months of age. Fetal deaths were observed in l4%,24% and 15% of pregnant females monkeys in the 0, 5 and 150 mglkg groups, respectively. Infant deaths occurred with an incidence of 0%, 8% and 5%. The cause of fetal and infant deaths in monkeys is not known. The relevance of these findings to humans is not known.

BENLYSTA should not be used during pregnancy unless clearly necessary.

Women of child-bearing potential must use effective contraception during BENLYSTA treatment and for at least 4 months after the last treatment.

Use in Lactation:

It is unknown whether BENLYSTA is excreted in human milk or is absorbed systemically after ingestion. However, belimumab was detected in the milk from female cynomolgus monkeys administered 150 mg/kg every 2 weeks.

Because maternal antibodies (IgG) are excreted in breast milk, it is recommended that a decision should be made whether to discontinue breast-feeding or to discontinue BENLYSTA therapy, taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Paediatric Use:

The safety and efficacy of BENLYSTA in children below 18 years of age have not yet been established. No data are available.

Use in the Elderly:

No substantial differences were seen in safety and efficacy related to age (see *DOSAGE AND ADMINISTRATION*). However, there is insufficient experience in this age group to draw firm conclusions.

Carcinogenicity:

The carcinogenic potential of BENLYSTA has not been investigated.

Genotoxicity:

As belimumab is a monoclonal antibody, no genotoxicity studies have been conducted.

Interactions with other medicines:

No interaction studies have been performed.

In clinical trials of patients with SLE, BENLYSTA was administered concomitantly with other drugs, including corticosteroids, antimalarials, immunomodulatory and immunosuppressive agents (including azathioprine, methotrexate, and mycophenolate), angiotensin pathway antihypertensives, HMG-CoA reductase inhibitors (statins), and NSAIDs without evidence of a clinically meaningful effect of these concomitant medications on belimumab pharmacokinetics.

Effect on Laboratory Tests:

No data available.

Ability to Drive and Use Machines:

No studies on the effects on the ability to drive and use machines have been performed.

ADVERSE EFFECTS

The safety of BENLYSTA in patients with SLE has been evaluated in three placebo-controlled studies.

The data described below reflect exposure to BENLYSTA in 674 patients with SLE, including 472 exposed for up to 52 weeks. Patients received belimumab 10 mg/kg intravenously over a 1-hour period on Days 0, 14, 28, and then every 28 days for 52 weeks.

The majority of patients were also receiving one or more of the following concomitant treatments for SLE: corticosteroids, immunomodulatory agents, anti-malarials, non-steroidal anti-inflammatory drugs.

Tabulated summary of adverse reactions

Adverse reactions are listed below by MedDRA body system organ class and by frequency. The frequency categories used are:

Very common ≥ 1 in 10
Common ≥ 1 in 100 and < 1 in 10
Uncommon ≥ 1 in 1,000 and < 1 in 100

System Organ Class	Frequency	Adverse Reaction(s)
Infections and infestations	Very common	Infections (non-opportunistic)
Immune System Disorders	Common	Hypersensitivity reactions*
	Uncommon	Anaphylactic reaction, angioedema
Skin and Subcutaneous Tissue Disorders	Uncommon	Rash Urticaria
General Disorders and Administration Site Conditions	Common	Pyrexia, infusion-related reaction

* Hypersensitivity reactions covers a group of terms, including anaphylaxis, and can manifest as a range of symptoms including hypotension, angioedema, urticaria or other rash, pruritus, and dyspnoea. 'Infusion-related reaction' covers a group of terms and can manifest as a range of symptoms including bradycardia, myalgia, headache, rash, urticaria, pyrexia, hypotension, hypertension, dizziness, and arthralgia. Due to overlap in signs and symptoms, it is not possible to distinguish between hypersensitivity reactions and infusion reactions in all cases.

The incidence of infusion reactions and hypersensitivity reactions occurring during or on the same day as an infusion was 17% in the group receiving BENLYSTA and 15% in the group receiving placebo, with 1% and 0.3%, respectively, requiring permanent treatment discontinuation. These reactions were generally observed on the day of the infusion, and patients with a history of multiple drug allergies or significant hypersensitivity reactions may be at increased risk. Delay in the onset of acute hypersensitivity reactions for several hours after infusion, and recurrence of clinically significant reactions after initial resolution of symptoms following appropriate treatment, have been observed.

Infections: In clinical studies, the overall incidence of infections was 70% in the group receiving BENLYSTA and 67% in the group receiving placebo. Infections occurring in at least 3% of patients receiving BENLYSTA and at least 1% more frequently than patients receiving placebo were nasopharyngitis, bronchitis, pharyngitis, cystitis, and gastroenteritis viral. Serious infections occurred in 5% of patients receiving either BENLYSTA or placebo.

The following table lists the most common (>10%) adverse events by MedRA preferred term.

Most common (>10% in any treatment group) adverse events by MeDRA preferred term

Preferred Term	**Placebo N = 675**	**BENLYSTA N = 674**
Headache	140 (20.7%)	142 (21.1%)
Upper respiratory tract infection	130 (19.3%)	118 (17.5%)
Arthralgia	112 (16.6%)	109 (16.2%)
Nausea	82 (12.1%)	99 (14.7%)
Urinary Tract Infection	82 (12.1%)	87 (12.9%)
Diarrhoea	62 (9.2%)	80 (11.9%)
Fatigue	70 (10.4%)	66 (9.8%)

Adverse events occurring in at least 3% of patients treated with belimumab 10 mg/kg plus standard of care and at least 1% more frequently than in patients receiving placebo plus standard of care in 3 controlled SLE studies

Preferred Term	Belimumab 10 mg/kg + Standard of Care (n = 674) %	Placebo + Standard of Care (n = 675) %
Nausea	15	12
Diarrhoea	12	9
Pyrexia	10	8
Nasopharyngitis	9	7
Bronchitis	9	5
Insomnia	7	5
Pain in extremity	6	4
Depression	5	4
Migraine	5	4
Pharyngitis	5	3
Cystitis	4	3
Leukopenia	4	2
Gastroenteritis viral	3	1

DOSAGE AND ADMINISTRATION

BENLYSTA treatment should be initiated and supervised by a healthcare professional experienced in the diagnosis and treatment of SLE. BENLYSTA infusions should be administered in an environment where full resuscitation facilities are available, and under the close supervision of an experienced healthcare professional.

BENLYSTA is administered intravenously by infusion, and must be reconstituted and diluted prior to administration (*see USE AND HANDLING*).

BENLYSTA should be infused over a 1-hour period.

BENLYSTA must not be administered as an intravenous push or bolus.

The infusion rate may be slowed or interrupted if the patient develops an infusion reaction. The infusion must be discontinued immediately if the patient experiences a potentially life-threatening adverse reaction (see *PRECAUTIONS*).

Patients should be monitored during and for an appropriate period of time after administration of BENLYSTA (see *PRECAUTIONS* and *ADVERSE EFFECTS*).

There is limited data to support the benefit or durability of treatment beyond 52 weeks (see *CLINICAL TRIALS*). It is recommended to regularly monitor the patient to ensure continued benefit/durability of treatment are maintained.

Discontinuation of treatment with BENLYSTA should be considered if there is no improvement in disease control after 6 months of treatment

Premedication

Premedication with an oral antihistamine, with or without an antipyretic, may be administered before the infusion of belimumab. There is insufficient evidence to determine whether premedication diminishes the frequency or severity of infusion reactions.

Adults

The recommended dosage regimen is 10 mg/kg BENLYSTA on Days 0, 14 and 28, and at 4-week intervals thereafter. Discontinuation of treatment with Benlysta should be considered if there is no improvement in disease control after 6 months of treatment. Beyond 52 weeks of treatment the physician should regularly monitor the patient to ensure benefit and durability of treatment are maintained (see clinical trials sections).

Children

The safety and efficacy of BENLYSTA in children below 18 years of age have not yet been established. No data are available.

Elderly (>65 years)

Although data are limited, dosage adjustment is not recommended (see *Pharmacokinetics – Special patient populations*).

Renal impairment

No formal studies with BENLYSTA have been performed in patients with renal impairment.

BENLYSTA has been studied in a limited number of SLE patients with renal impairment. On the basis of the available information, dosage adjustment is not required in patients with mild, moderate or severe renal impairment. Caution is however recommended in

patients with severe renal impairment due to the limited data available (see *Pharmacokinetics – Special patient populations*).

Hepatic impairment

No formal studies with BENLYSTA have been conducted in patients with hepatic impairment. However, patients with hepatic impairment are unlikely to require dose modification (see *Pharmacokinetics – Special patient populations*).

USE AND HANDLING

Reconstitution and dilution

BENLYSTA does not contain a preservative; therefore reconstitution and dilution must be carried out under aseptic conditions.

Allow 10-15 minutes for the vial to warm to room temperature.

The 120 mg single-use vial of BENLYSTA is reconstituted with 1.5 mL of sterile Water for Injections to yield a final concentration of 80 mg/mL belimumab. The 400 mg single-use vial of BENLYSTA is reconstituted with 4.8 mL of sterile Water for Injections to yield a final concentration of 80 mg/mL belimumab.

The stream of sterile water should be directed toward the side of the vial to minimize foaming. Gently swirl the vial for 60 seconds. Allow the vial to sit at room temperature during reconstitution, gently swirling the vial for 60 seconds every 5 minutes until the powder is dissolved. **DO NOT SHAKE**. Reconstitution is typically complete within 10 to 15 minutes after the sterile water has been added, but it may take up to 30 minutes. Protect the reconstituted solution from sunlight.

If a mechanical reconstitution device is used to reconstitute BENLYSTA it should not exceed 500 rpm and the vial should be swirled for no longer than 30 minutes.

Once reconstitution is complete, the solution should be opalescent and colorless to pale yellow and without particles. Small air bubbles, however, are expected and acceptable.

The reconstituted product is diluted to 250 mL with 0.9% normal saline for IV infusion.

5% Glucose IV solutions are incompatible with BENLYSTA and should not be used.

From a 250 mL infusion bag or bottle of normal saline, withdraw and discard a volume equal to the volume of the reconstituted BENLYSTA solution required for the patient's dose. Then add the required volume of the reconstituted BENLYSTA solution into the infusion bag or bottle. Gently invert the bag or bottle to mix the solution. Any unused solution in the vials must be discarded.

Inspect the BENLYSTA solution visually for particulate matter and discoloration prior to administration. Discard the solution if any particulate matter or discoloration is observed.

The reconstituted solution, if not used immediately, should be protected from direct sunlight and stored refrigerated at 2-8°C. Solutions diluted in normal saline may be stored at 2-8°C or room temperature.

BENLYSTA does not contain a preservative and is for single use in one patient only. Therefore it is recommended that the diluted solution be used as soon as possible after preparation. The total time from reconstitution of BENLYSTA to completion of infusion should not exceed 8 hours. Any unused solution remaining after this time should be discarded.

Administration

BENLYSTA is infused over a 1 hour period.
BENLYSTA should not be infused concomitantly in the same intravenous line with other agents. No physical or biochemical compatibility studies have been conducted to evaluate the co-administration of BENLYSTA with other agents.

No incompatibilities between BENLYSTA and polyvinylchloride or polyolefin bags have been observed.

Disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

OVERDOSAGE

There is no clinical experience with overdosage of BENLYSTA.

Two doses up to 20 mg/kg administered 21 days apart by intravenous infusion have been given to humans with no increase in incidence or severity of adverse reactions compared with doses of 1, 4, or 10 mg/kg.

In the case of inadvertent overdose, patients should be carefully observed and supportive care administered, as appropriate.

PRESENTATION AND STORAGE CONDITIONS

Shelf Life

Unopened vials

36 months. Store at 2°C to 8°C (Refrigerate. Do not freeze.)
Protect from light. Store in the original carton until use.

Reconstituted solution

After reconstitution with sterile Water for Injections, the reconstituted solution, if not used immediately, should be protected from direct sunlight, and stored refrigerated at 2- 8°C and must be used within 7 hours.

Reconstituted and diluted solution for infusion

Solutions of BENLYSTA diluted in normal saline may be stored at 2- 8°C or room temperature.

BENLYSTA does not contain a preservative and is for single use in one patient only. Therefore it is recommended that the diluted solution be used as soon as possible after preparation. The total time from reconstitution of BENLYSTA to completion of infusion should not exceed 8 hours. The 8 hour time period includes a 1 hour infusion time plus up to 7 hours either as a reconstituted solution of BENLYSTA stored protected from direct sunlight and refrigerated at 2° to 8°C or as a solution of BENLYSTA diluted in normal saline and stored at 2° to 8°C or room temperature. Any unused solution remaining after this time should be discarded.

Presentation

BENLYSTA is supplied as a lyophilized formulation for infusion in sterile, single-use, Type 1 glass vials, sealed with a latex-free, siliconised rubber stopper and a flip-off aluminum seal.

Each 5 mL vial delivers 120 mg of BENLYSTA.

Each 20 mL vial delivers 400 mg of BENLYSTA.

BENLYSTA is available in packs of 1 x 5 mL or 1 x 20 ml vials.

*Not all pack sizes may be marketed.

NAME AND ADDRESS OF THE SPONSOR

GlaxoSmithKline Australia Pty Ltd
Level 4, 436 Johnston Street

Abbotsford, Victoria 3067
Australia

POISON SCHEDULE OF THE MEDICINE

Schedule 4 – Prescription Only Medicine

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG): 19 October 2012

DATE OF MOST RECENT AMENDMENT: 19 October 2012

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