BENLYSTA

Belimumab

QUALITATIVE AND QUANTITATIVE COMPOSITION

120 mg vial

Each vial contains 120 mg belimumab (80 mg/mL after reconstitution).

400 mg vial

Each vial contains 400 mg belimumab (80 mg/mL after reconstitution).

Belimumab is a human, IgG1λ monoclonal antibody specific for soluble human B Lymphocyte Stimulator protein (BLyS). Belimumab is produced by recombinant DNA technology in a mammalian cell expression system.

CLINICAL INFORMATION

Indications

BENLYSTA is indicated for:

- reducing disease activity in patients aged 5 years and older with active autoantibody positive systemic lupus erythematosus (SLE) who are receiving standard therapy.
- treatment of lupus nephritis in adult patients who are receiving standard therapy.

Dosage and Administration

Powder for concentrate for solution for infusion.

White to off-white powder.

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

BENLYSTA should be administered by a healthcare professional prepared to treat hypersensitivity reactions including anaphylaxis.

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 Contraindications, Warnings and Precautions*).

Patients should be monitored during and for an appropriate period of time after administration of *BENLYSTA* (see *Warnings and Precautions, Adverse Reactions*).

Premedication for patients with allergies

Premedication with an oral antihistamine, with or without an antipyretic, may be administered before the infusion of *BENLYSTA* (see *Warnings and Precautions, Clinical Studies*).

Adults

SLE

The recommended dosage regimen is 10 mg/kg 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.

Lupus nephritis

The recommended dosage regimen is 10 mg/kg on Days 0, 14 and 28, and at 4-week intervals thereafter.

Children

SLE

The recommended dosage regimen for children aged 5 years and older is 10 mg/kg 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.

The safety and efficacy of *BENLYSTA* in children below 5 years of age have not been studied, therefore, *BENLYSTA* is not recommended for use in children under 5 years old with SLE.

Lupus nephritis

The safety and efficacy of *BENLYSTA* in children and adolescents aged below 18 years have not been studied, therefore, *BENLYSTA* is not recommended for use in children and adolescents with active lupus nephritis.

Elderly

Although data are limited, dosage adjustment is not recommended (*see Pharmacokinetics - Special Patient Groups*).

Renal impairment

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

BENLYSTA has been studied in a limited number of SLE patients with renal impairment. Dosage adjustment is not required in patients with renal impairment (*see Pharmacokinetics - Special Patient Groups*).

Hepatic impairment

No formal studies of *BENLYSTA* have been performed in patients with hepatic impairment. However, patients with hepatic impairment are unlikely to require dose modification (*see Pharmacokinetics - Special Patient Groups*).

Contraindications

BENLYSTA is contraindicated in patients who have demonstrated anaphylaxis to *BENLYSTA*.

Warnings and Precautions

Concomitant use with B cell targeted therapy

BENLYSTA has not been studied in combination with other B cell targeted therapy. Caution should be exercised if *BENLYSTA* is co-administered with other B cell targeted therapy.

Infusion reactions and hypersensitivity

Administration of *BENLYSTA* may result in infusion and hypersensitivity 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. Patients with a history of multiple drug allergies or significant hypersensitivity may be at increased risk (*see Adverse Reactions*).

Premedication with an oral antihistamine, with or without an antipyretic, may be administered before the infusion of *BENLYSTA*. There is insufficient evidence to determine whether premedication diminishes the frequency or severity of infusion reactions. In clinical trials, serious infusion and hypersensitivity reactions affected less than 1% of patients, and included anaphylactic reaction, bradycardia, hypotension,

angioedema, and dyspnoea. Infusion reactions occurred more frequently on 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 *BENLYSTA* should be made aware of the potential risk, the signs and symptoms of such reactions, and the importance of immediately seeking medical attention. Delayed-type, non-acute hypersensitivity reactions have also been observed and included symptoms such as rash, nausea, fatigue, myalgia, headache, and facial oedema.

Risk of infections

As with other immunomodulating agents, the mechanism of action of *BENLYSTA* may increase the risk for the development of infections. In controlled clinical studies, fatal infections were uncommon, but occurred more frequently in patients receiving BENLYSTA compared with placebo. Overall, the incidence of serious infections was similar across the BENLYSTA and placebo groups (*see Adverse Reactions*). Patients who develop an infection while undergoing treatment with *BENLYSTA* should be monitored closely, and consideration should be given to stopping immunosuppressant therapy. Physicians should exercise caution when considering the use of *BENLYSTA* in patients with severe or chronic infections.

Depression and suicidality

In controlled clinical intravenous and subcutaneous studies, psychiatric disorders (depression, suicidal ideation and behaviour) have been reported more frequently in patients receiving *BENLYSTA* including one suicide in a patient receiving 10 mg/kg and one suicide in a patient receiving 1 mg/kg (*see Adverse Reactions*). Physicians should carefully assess the risk of depression and suicide considering the patient's medical history and current psychiatric status before treatment with *BENLYSTA*, and continue to monitor patients during treatment. Physicians should advise patients (and caregivers where appropriate) to contact their health care provider about new or worsening psychiatric symptoms. The risk and benefit of continued treatment with *BENLYSTA* should be carefully assessed for patients who develop such symptoms.

Progressive multifocal leukoencephalopathy (PML)

Progressive multifocal leukoencephalopathy (PML) resulting in neurological deficits, including fatal cases, has been reported in SLE patients receiving immunosuppressant pharmacotherapy, including *BENLYSTA*. A diagnosis of PML should be considered in any patient presenting with new-onset or deteriorating neurological signs and symptoms. The patient should be referred to a neurologist or other appropriate specialist for evaluation and if PML is confirmed, consideration should be given to stopping immunosuppressant therapy, including *BENLYSTA*.

Risk of malignancies

As with other immunomodulating agents, the mechanism of action of *BENLYSTA* may increase the potential risk for the development of malignancies. In clinical trials, there

was no difference in the rate of malignancies between *BENLYSTA*-treated and placebo-treated groups.

Immunisation

Live vaccines should not be given for 30 days before, or 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. However, in a study evaluating the response to a 23-valent pneumococcal vaccine, overall immune responses to the different serotypes were similar in SLE patients receiving belimumab compared with those not receiving treatment at the time of vaccination.

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*.

Interactions

No drug interaction studies have been conducted with *BENLYSTA*.

In clinical trials of patients with SLE, concomitant administration of mycophenolate mofetil, cyclophosphamide, azathioprine, hydroxychloroquine, methotrexate, non-steroidal anti-inflammatory medications, aspirin, and HMG CoA reductase inhibitors had no significant effect on belimumab exposures (*see Pharmacokinetics*).

Pregnancy and Lactation

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 (*see Non-clinical Information*).

Pregnancy

There are limited data on the use of *BENLYSTA* in pregnant women. No formal studies have been conducted. Immunoglobulin G (IgG) antibodies, including belimumab, can cross the placenta. *BENLYSTA* should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

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

Animal studies did not indicate direct or indirect harmful effects with respect to maternal toxicity, pregnancy or embryofoetal development. Treatment-related findings were limited to reversible reductions in B cells in infant monkeys *(see Non-clinical Information).* Monitor infants of treated mothers for B-cell reduction and depending upon the results, consider delaying infant vaccination with live viral vaccines. B-cell reduction in infants may also interfere with the response to immunisations (*see Warnings and Precautions*).

Lactation

The safety of *BENLYSTA* 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. Although belimumab was excreted into the milk of cynomolgous monkeys, published literature suggests that human neonatal and infant consumption of breast milk does not result in clinically significant absorption of maternal IgG antibodies into circulation.

It is recommended that a decision should be made about *BENLYSTA* therapy in breast-feeding mothers, taking into account 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 from belimumab or from the underlying maternal condition.

Effects on Ability to Drive and Use Machines

There have been no studies to investigate the effect of *BENLYSTA* on driving performance or the ability to operate machinery. No detrimental effects on such activities are predicted from the pharmacology of *BENLYSTA*.

The clinical status of the patient and the safety profile of *BENLYSTA* should be borne in mind when considering the patient's ability to perform tasks that require judgement, motor or cognitive skills.

Adverse Reactions

Adults

The safety of *BENLYSTA* in patients with SLE has been evaluated in three pre-registration placebo-controlled intravenous studies, one placebo-controlled subcutaneous study, and one post-marketing placebo-controlled intravenous study; the safety in patients with active lupus nephritis has been evaluated in one placebo-controlled intravenous study.

The data described below reflect exposure in 674 patients with SLE administered *BENLYSTA* intravenously (10 mg/kg over a 1-hour period on Days 0, 14, 28, and then every 28 days up to 52 weeks), and 556 patients with SLE administered *BENLYSTA* subcutaneously (200 mg once weekly up to 52 weeks). The safety data presented include data beyond Week 52 in some patients with SLE. The data reflect additional exposure in

224 patients with active lupus nephritis who received *BENLYSTA* intravenously (10 mg/kg for up to 104 weeks). Data from post-marketing reports are also included.

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. 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

MedDRA SOC	**Very common:**	**Common:**	**Uncommon:**
Infections and infestations	Infections		
Immune System Disorders		Hypersensitivity reaction*	Anaphylactic reaction Angioedema
Psychiatric disorders		Depression	Suicidal ideation Suicidal behaviour
Skin and Subcutaneous Tissue Disorders			Rash Urticaria
General Disorders and Administration Site Conditions		Pyrexia Infusion related systemic reactions*	

*'Hypersensitivity reaction' covers a group of terms, including anaphylaxis, and can manifest as a range of symptoms including hypotension, angioedema, urticaria or other rash, pruritus, and dysponea. '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.

Hypersensitivity reactions: Clinically significant hypersensitivity reactions associated with *BENLYSTA* and requiring permanent treatment discontinuation were reported in 0.4% of patients. 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 the infusion, and recurrence of clinically significant reactions after initial resolution of symptoms following appropriate treatment, have been observed. Delayed-type, non-acute hypersensitivity reactions have also been observed and included symptoms such as rash, nausea, fatigue, myalgia, headache, and facial oedema.

Infections: In the intravenous SLE pre-registration clinical sudies, the overall incidence of infections was 70% in the group receiving belimumab 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 belimumab or placebo; serious opportunistic infections accounted for <1% and 0% of these, respectively. Some infections were severe or fatal.

In the randomised (1:1), double-blind, placebo-controlled, 52-week, post-marketing SLE safety study (BEL115467) which assessed mortality and specific adverse events in adults, serious infections occurred in 3.7% of patients receiving *BENLYSTA* 10 mg/kg intravenously and in 4.1% of patients receiving placebo. Fatal infections occurred in 0.45% (9/2002) of patients receiving *BENLYSTA* and in 0.15% (3/2001) of patients receiving placebo, while the incidence of all-cause mortality was 0.50% (10/2002) in patients receiving belimumab and 0.40% (8/2001) in patients receiving placebo.

In the lupus nephritis study, patients were receiving a background of standard therapy (*see Clinical Studies*) and the overall incidence of infections was 82% in patients receiving *BENLYSTA* compared with 76% in patients receiving placebo. Serious infections occurred in 13.8% of patients receiving *BENLYSTA* and in 17.0% of patients receiving placebo. Fatal infections occurred in 0.9% (2/224) of patients receiving *BENLYSTA* and in 0.9% (2/224) of patients receiving placebo.

Psychiatric disorders: In the pre-registration SLE intravenous clinical studies, serious psychiatric events were reported in 1.2% (8/674) of patients receiving *BENLYSTA* 10 mg/kg and 0.4% (3/675) of patients receiving placebo. Serious depression was reported in 0.6% (4/674) of patients receiving *BENLYSTA* 10 mg/kg and 0.3% (2/675) of patients receiving placebo. One suicide was reported in a patient receiving *BENLYSTA* 10 mg/kg (and one was reported in a patient receiving *BENLYSTA* 1 mg/kg); there were no reports in patients receiving placebo.

In the large post-marketing SLE study, serious psychiatric events were reported in 1.0% (20/2002) of patients receiving *BENLYSTA* and 0.3% (6/2001) of patients receiving placebo. Serious depression was reported in 0.3% (7/2002) of patients receiving *BENLYSTA* and <0.1% (1/2001) receiving placebo. The overall incidence of serious suicidal ideation or behaviour or self-injury without suicidal intent was 0.7% (15/2002) in the *BENLYSTA* group and 0.2% (5/2001) in the placebo group. On the Columbia-Suicide Severity Rating Scale (C-SSRS), 2.4% (48/1974) of patients receiving *BENLYSTA* reported suicidal ideation or behaviour compared with 2.0% (39/1988) of patients receiving placebo. No suicide was reported in either group.

The SLE intravenous studies did not exclude patients with a history of psychiatric disorders.

In the subcutaneous SLE clinical study, which excluded patients with a history of psychiatric disorders, serious psychiatric events were reported in 0.2% (1/556) of patients receiving *BENLYSTA* and in no patients receiving placebo. There were no serious depression-related events or suicides reported in either group. On the C-SSRS, 1.3% (7/554) of patients receiving *BENLYSTA* reported suicidal ideation or behaviour and 0.7% (2/277) of patients receiving placebo.

Children aged 5 and older

The adverse reaction profile in paediatric patients is based on 52 week safety data from a placebo controlled study in which 53 patients with SLE received *BENLYSTA* intravenously (10 mg/kg) on Days 0, 14, 28, and then every 28 days, on a background of concomitant treatments. The safety profile in paediatric patients was consistent with that observed in clinical studies in adult patients.Overdose

There is limited experience with overdosage of *BENLYSTA.* Adverse reactions reported in association with cases of overdose have been consistent with those expected for belimumab.

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.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics

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, leading to elevated plasma BLyS levels. 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 Effect

In adult patients with SLE, 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 hypergammaglobulinaemia at baseline, normalisation 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 SLE with low complement levels at baseline, belimumab treatment resulted in increases in complement C3 and C4 which were seen as early as Week 4 and continued over time. By Week 52, levels of C3 and C4 had normalised 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.

In a long-term uncontrolled extension SLE study, B cells (including naïve, activated, plasma cells and the SLE B cell subset) and IgG levels were followed for more than 7 years with ongoing treatment. A substantial and sustained decrease in various B cell subsets was observed leading to median reductions of 87% in naive B cells, 67% in memory B cells, 99% in activated B cells, and 92% in plasma cells after more than 7 years of treatment. After about 7 years, a 28% median reduction in IgG levels was observed with 1.6% of subjects experiencing a decrease in IgG levels to below 400 mg/dL. Over the course of the study, the reported incidence of AEs generally remained stable or declined.

In patients with active lupus nephritis, following treatment with belimumab or placebo, there was an increase in serum IgG levels which was associated with decreased proteinuria. Relative to placebo, smaller increases in serum IgG levels were observed in the belimumab group as expected with the known mechanism of belimumab. At Week 104, the median percent increase from baseline in IgG was 17% for belimumab and 37% for placebo. Reductions in autoantibodies, increases in complement, and reductions in circulating total B cells and B-cell subsets observed were consistent with the SLE studies.

In a Phase II study in paediatric patients with SLE the pharmacodynamic response was consistent with the adult data.**Immunogenicity:**

In the two Phase III SLE studies with *BENLYSTA* administered intravenously in adult patients, 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 three patients receiving belimumab 1 mg/kg.

In a Phase III/IV study with *BENLYSTA* 10 mg/kg administered intravenously to black patients, two of the 321 (0.6%) patients developed anti-belimumab antibodies.

In a Phase III study with *BENLYSTA* 10 mg/kg administered intravenously to adult patients with active lupus nephritis, none of the 224 patients developed anti-belimumab antibodies.

In a Phase II study in paediatric patients none of the 53 patients developed anti-belimumab antibodies.

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

SLE studies

The pharmacokinetic parameters below are based on population parameter estimates which are specific to the 563 patients with SLE who received belimumab 10 mg/kg (Days 0, 14, 28, and then every 28 days up to 52 weeks) in the two Phase III studies in adults.

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 313 micrograms/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 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 1.75 days and terminal half-life 19.4 days. The systemic clearance was 215 mL/day.

Lupus nephritis study

A population pharmacokinetic analysis was conducted in 224 adult patients with lupus nephritis who received *BENLYSTA* 10 mg/kg intravenously (Days 0, 14, 28, and then every 28 days up to 104 weeks). In patients with lupus nephritis, due to renal disease activity, belimumab clearance was initially higher than observed in SLE studies; however, after 24 weeks of treatment and throughout the remainder of the study, belimumab clearance and exposure were similar to that observed in adult patients with SLE who received *BENLYSTA* 10 mg/kg intravenously.

Drug interactions

Concomitant use of mycophenolate mofetil, cyclophosphamide, azathioprine, methotrexate and hydroxychloroquine did not substantially influence belimumab pharmacokinetics based on the results of the population pharmacokinetic analysis. Neither did a wide range of other co-medications (non-steroidal anti-inflammatory medications, aspirin, and HMG-CoA reductase inhibitors) significantly influence belimumab pharmacokinetics. Co-administration of steroids and ACE inhibitors resulted in a statistically significant increase of systemic clearance in the population pharmacokinetic analysis. However, these effects were not clinically meaningful as their magnitude was well within the range of normal variability of clearance.

Special Patient Groups

Elderly

Belimumab has been studied in a limited number of elderly patients. Within the overall SLE intravenous study population, age did not affect belimumab exposure in the population pharmacokinetic analysis. However, given the small number of subjects 65 years or older, an effect of age cannot be ruled out conclusively.

Children and adolescents

The pharmacokinetic parameters are based on population parameter estimates of 53 patients from a Phase II study in paediatric patients. Following IV administration of 10 mg/kg on Days 0, 14 and 28, and at 4-week intervals thereafter, belimumab exposures were similar between paediatric and adult SLE subjects. Steady-state geometric mean Cmax and AUC values were 305 and 2569 day●g/mL in the 5-11 year old group, and 317 and 3126 day●µg/mL in the 12-17 year old group.

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 less than 60 mL/min, including a small number with creatinine clearance less than 30 mL/min). Although proteinuria (greater than or equal to 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 normalised dosing.

Clinical Studies

SLE

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 (ACR) classification criteria. Eligible patients had active SLE disease, defined as a SELENA-SLEDAI score greater than or equal to 6 and positive anti-nuclear antibody (ANA or anti-dsDNA) test results (ANA titre greater than or equal to 1:80 and/or a positive anti-dsDNA [greater than or equal to 30 units/mL]) at screening. Patients were on a stable SLE treatment r egimen (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 Study 1 was a 76-week study and Study 2 was a 52-week study. Both studies had 52-week primary endpoints.

Study 1 (HGS1006-C1056) 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%).

Study 2 (HGS1006-C1057) 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 (less than or equal to 9 vs greater than or equal to 10), proteinuria level (less than 2 g per 24 hr vs greater than or equal to 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:

- greater than or equal to 4-point reduction in the SELENA-SLEDAI score, and
- no new British Isles Lupus Assessment Group (BILAG) A organ domain score or *two* new BILAG B organ domain scores, and
- no worsening (less than 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

Response	Study 1		Study 2		Studies 1 and 2 Pooled	
	Placebo (n=275)	*BENLYSTA* 10mg/kg (n=273)	Placebo (n=287)	*BENLYSTA* 10mg/kg (n=290)	Placebo (n=562)	*BENLYSTA* 10mg/kg (n=563)
SLE Responder Index	33.8%	43.2% (P=0.021	43.6%	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%	46.9% (P=0.006)	46.0%	58.3% (P= 0.0024)	40.9%	52.8% (P<0.0001)
Percent of patients with no worsening by BILAG index	65.1%	69.2% (P=0.32)	73.2%	81.4% (P=0.018)	69.2%	75.5% (P=0.019)
Percent of patients with no worsening by PGA	62.9%	69.2% (P=0.13)	69.3%	79.7% (P=0.0048)	66.2%	74.6% (P=0.0017)

In a pooled analysis of the two studies, the percentage of patients receiving greater than 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 less than or equal to 7.5 mg/day during Weeks 40 through 52, was 17.9% in the group receiving belimumab and 12.3% 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 greater than 12. The median time to the first flare was delayed in the

pooled group receiving belimumab compared to the group receiving placebo (hazard ratio= 0.84, P=0.012). The risk of severe flares was also reduced by 36% over the 52 weeks of observation in the group receiving belimumab compared to the group receiving placebo (hazard ratio=0.64, P=0.0011).

Univariate and multivariate analysis of the primary endpoint demonstrated that the greatest benefit was observed in patients with higher disease activity including patients with SELENA SLEDAI scores greater than or equal to 10, or patients requiring steroids to control their disease, or patients with low complement levels.

Post-hoc analysis identified a high responding subgroup as those patients with low complement and positive anti-dsDNA at baseline, see Table 2 for results of this example of a higher disease activity group. Of these patients, 64.5% had SELENA SLEDAI scores greater than or equal to 10 at baseline.

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 greater than 7.5 mg/day

Lupus nephritis

The efficacy and safety of *BENLYSTA* 10 mg/kg administered intravenously over a 1-hour period on Days 0, 14, 28, and then every 28 days, were evaluated in a 104-week randomised (1:1), double-blind, placebo-controlled, Phase III study (BEL114054) in

448 patients with active lupus nephritis. The patients had a clinical diagnosis of SLE according to ACR classification criteria, biopsy-proven lupus nephritis Class III, IV, and/or V and had active renal disease at screening requiring standard therapy (corticosteroids with [1] mycophenolate mofetil for induction and maintenance, or [2] cyclophosphamide for induction followed by azathioprine for maintenance). This study was conducted in Asia, North America, South America, and Europe. Patient median age was 31 years (range: 18 to 77 years); the majority (88%) of patients were female.

The primary efficacy endpoint was Primary Efficacy Renal Response (PERR) at Week 104 defined as a response at Week 100 confirmed by a repeat measurement at Week 104 of the following parameters: urinary protein:creatinine ratio (uPCR) ≤0.7 and estimated glomerular filtration rate (eGFR) ≥60 mL/min/1.73m^2 or no decrease in eGFR of >20% from pre-flare value.

The major secondary endpoints included:

- Complete Renal Response (CRR) defined as a response at Week 100 confirmed by a repeat measurement at Week 104 of the following parameters: uPCR <0.5 and eGFR ≥90 mL/min/1.73m^2 or no decrease in eGFR of >10% from pre-flare value.
- PERR at Week 52.
- Time to renal-related event or death (renal-related event defined as first event of end-stage renal disease, doubling of serum creatinine, renal worsening [defined as increased proteinuria, and/or impaired renal function], or receipt of renal disease-related prohibited therapy).

For PERR and CRR endpoints, steroid treatment had to be reduced to ≤10 mg/day from Week 24 to be considered a responder. For these endpoints, patients who discontinued treatment early, received prohibited medication, or withdrew from the study early were considered non-responders.

The proportion of patients achieving PERR at Week 104 was significantly higher in patients receiving belimumab compared with placebo. The major secondary endpoints also showed significant improvement with *BENLYSTA* compared with placebo (Table 3).

Table 3: Efficacy results in adult patients with lupus nephritis

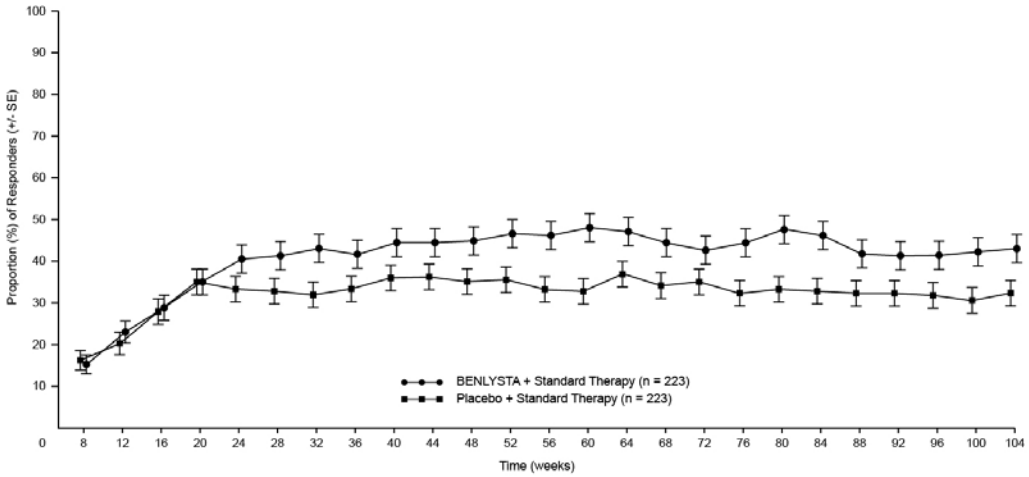
Efficacy Endpoint	Placebo N=223	*BENLYSTA* 10 mg/kg N=223	Observed difference vs placebo	Odds/ Hazard ratio vs. placebo (95% CI)	P-value
PERR at Week 104[1] Responders	32.3%	43.0%	10.8%	OR 1.55 (1.04, 2.32)	0.0311
Components of PERR					
Urine protein:creatinine ratio ≤0.7	33.6%	44.4%	10.8%	OR 1.54 (1.04, 2.29)	0.0320
eGFR≥60 mL/min/1.73m^2 or no decrease in eGFR from pre-flare value of >20%	50.2%	57.4%	7.2%	OR 1.32 (0.90, 1.94)	0.1599
Not treatment failure[3]	74.4%	83.0%	8.5%	OR 1.65 (1.03, 2.63)	0.0364
CRR at Week 104[1] Responders	19.7%	30.0%	10.3%	OR 1.74 (1.11, 2.74)	0.0167
Components of CRR					
Urine protein:creatinine ratio <0.5	28.7%	39.5%	10.8%	OR 1.58 (1.05, 2.38)	0.0268
eGFR≥90 mL/min/1.73m^2 or no decrease in eGFR from pre-flare value of >10%	39.9%	46.6%	6.7%	OR 1.33 (0.90, 1.96)	0.1539
Not treatment failure[3]	74.4%	83.0%	8.5%	OR 1.65 (1.03, 2.63)	0.0364
PERR at Week 52[1] Responders	35.4%	46.6%	11.2%	OR 1.59 (1.06, 2.38)	0.0245
Time to Renal-Related Event or Death[1] Percentage of patients with event[2]	28.3%	15.7%	-		
Time to event [Hazard ratio (95% CI)]			-	0.51 (0.34, 0.77)	0.0014

[1]PERR at Week 104 was the primary efficacy analysis; CRR at Week 104, PERR at Week 52 and time to renal-related event or death were included in the pre-specified testing hierarchy.
[2]When excluding deaths from the analysis (1 for *BENLYSTA*; 2 for placebo), the percentage of patients with a renal-related event was 15.2% for *BENLYSTA* compared with 27.4% for placebo (HR = 0.51; 95% CI: 0.34, 0.78).
[3]Treatment failure: Patients who took protocol-prohibited medication.

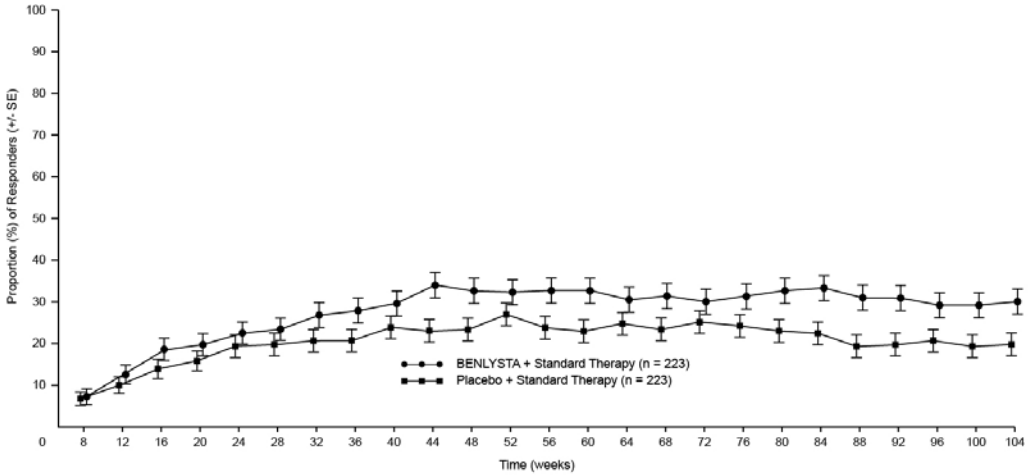
A numerically greater percentage of patients receiving *BENLYSTA* achieved PERR beginning at Week 24 compared with placebo, and this treatment difference was maintained through to Week 104. Beginning at Week 12, a numerically greater percentage of patients receiving *BENLYSTA* achieved CRR compared with placebo and the numerical difference was maintained through to Week 104 (Figure 1).

Figure 1. Response Rates in Adults with Lupus Nephritis by Visit

Primary Efficacy Renal Response (PERR)



Complete Renal Response (CRR)



Black patients

BENLYSTA was administered intravenously to black patients in a randomised (2:1), double blind, placebo-controlled 52-week Phase III/IV study (BEL115471). Efficacy was

evaluated in 448 patients. The study design was the same as the pivotal studies summarised above apart from: eligible patients had a SELENA-SLEDAI score ≥8 and the primary endpoint was the SRI response at Week 52 with modified SLEDAI-2K scoring for proteinuria (SRI-S2K). The study was conducted in North America, South America, Europe and Africa. Patient median age was 38 years (range: 18 to 71 years), and the majority of patients (97%) were female.

The proportion of black patients achieving an SRI-S2K response was higher in patients receiving *BENLYSTA* but the difference was not statistically significant compared with placebo. The trends in comparisons between the treatment groups for the rates of response for the individual components of the endpoint were generally consistent with that of the SRI-S2K (Table 4).

Table 4: Response rate in black patients at Week 52

Response	Placebo (n=149)	*BENLYSTA* 10 mg/kg (n=299)
SLE Responder Index (SRI-S2K) Odds ratio (95% CI) vs placebo	41.6%	48.7% 1.40 (0.93, 2.11) (P=0.1068)
Components of SLE Responder Index (SRI-S2K)		
Percent of patients with reduction in SELENA-SLEDAI-S2K ≥4 Odds ratio (95% CI) vs placebo	42.3%	50.0% 1.46 (0.97, 2.20)
Percent of patients with no worsening by BILAG index Odds ratio (95% CI) vs placebo	62.4%	67.8% 1.24 (0.81, 1.88)
Percent of patients with no worsening by PGA Odds ratio (95% CI) vs placebo	64.4%	69.5% 1.26 (0.82, 1.93)

The safety profile of *BENLYSTA* in black patients (n=331) was consistent with the known safety profile of *BENLYSTA* in the overall population.

Consistent with results from other studies, in patients with high disease activity (low complement and positive anti-dsDNA at baseline, n=141) the SRI-S2K response was 45.1% for *BENLYSTA* 10 mg/kg compared with 24.0% for placebo (odds ratio 3.00; 95% CI: 1.35, 6.68). These results suggest a greater relative response to *BENLYSTA* compared to placebo in black patients with high disease activity.

Other special patient groups

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

Paediatric patients

The safety and efficacy of *BENLYSTA* was evaluated in a randomised, double-blind, placebo-controlled 52-week Phase II study (BEL114055) in 93 paediatric patients with a clinical diagnosis of SLE according to the American College of Rheumatology classification criteria. Patients had active SLE disease, defined as a SELENA-SLEDAI score greater than or equal to 6 and positive anti-auto antibodies at screening as defined in the adult trials. Patients were on a stable SLE treatment regimen (standard of care) and had similar inclusion and exclusion criteria as the adult studies. This study was conducted in the US, South America, Europe, and Asia. Patient median age was 15.0 years (range 6 to 17 years). The majority (94.6%) of patients were female.

The primary efficacy endpoint was the SLE Responder Index (SRI) at Week 52 as described in the adult intravenous trials. There was a higher proportion of paediatric patients achieving an SRI response in patients receiving *BENLYSTA* compared with placebo. The response for the individual components of the endpoint were consistent with that of the SRI (Table 5). **Table 5 – Paediatric response rate at Week 52**

Response	Placebo (n=40)	*BENLYSTA* 10 mg/kg (n=53)
SLE Responder Index Odds ratio (95% CI) vs placebo	43.6%	52.8% 1.49 (0.64, 3.46)
Components of SLE Responder Index		
Percent of patients with reduction in SELENA-SLEDAI ≥4 Odds ratio (95% CI) vs placebo	43.6%	54.7% 1.62 (0.69, 3.78)
Percent of patients with no worsening by BILAG index Odds ratio (95% CI) vs placebo	61.5%	73.6% 1.96 (0.77, 4.97)
Percent of patients with no worsening by PGA Odds ratio (95% CI) vs placebo	66.7%	75.5% 1.70 (0.66, 4.39)

Paediatric patients taking *BENLYSTA* 10 mg/kg had a 64% lower risk of experiencing a severe flare compared with the placebo group (hazard ratio 0.36, 95% CI: 0.15, 0.86). Among patients experiencing a severe flare, the median study day of the first severe flare

was Day 113 in the placebo group and Day 150 in the *BENLYSTA* group. This was consistent with the findings from the adult intravenous clinical trials.

Using the Paediatric Rheumatology International Trials Organisation/American College of Rheumatology (PRINTO/ACR) Juvenile SLE Response Evaluation Criteria, a higher proportion of paediatric patients demonstrated improvement in patients receiving *BENLYSTA* compared with placebo (Table 6).

Table 6 – PRINTO/ACR response rate at Week 52

	The proportion of patients with at least 50% improvement in any 2 of 5 components* and no more than one of the remaining worsening by more than 30%		The proportion of patients with at least 30% improvement in 3 of 5 components* and no more than one of the remaining worsening more than 30%.	
	Placebo N=40	*BENLYSTA* 10 mg/kg N=53	Placebo N=40	*BENLYSTA* 10 mg/kg N=53
Response, n (%)	14/40 (35.0)	32/53 (60.4)	11/40 (27.5)	28/53 (52.8)
Observed difference vs Placebo		25.38		25.33
Odds ratio (95% CI) vs Placebo		2.74 (1.15, 6.54)		2.92 (1.19, 7.17)

*The five PRINTO/ACR components were percent change at Week 52 in: Parent's Global Assessment (Parent GA), PGA, SELENA SLEDAI score, 24-hour proteinuria, and, Paediatric Quality of Life Inventory – Generic Core Scale (PedsQL GC) physical functioning domain score

Non-Clinical Information

Non-clinical data revealed no special hazard for humans based on studies of repeated dose toxicity and toxicity to reproduction.

Intravenous and subcutaneous administration to monkeys resulted in the expected reduction in number of peripheral and lymphoid tissue B cell counts with no associated toxicological findings.

Reproductive studies have been performed in pregnant cynomolgus monkeys receiving belimumab 150 mg/kg by intravenous infusion (approximately nine times the anticipated maximum human clinical exposure) every two weeks for up to 21 weeks, and belimumab 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 three months of life in infant monkeys; IgM levels in infants exposed to belimumab in utero recovered by six months of age.

As belimumab is a monoclonal antibody, no genotoxicity studies have been conducted. No carcinogenicity or fertility studies (male or female) have been performed.

PHARMACEUTICAL INFORMATION

List of Excipients

Citric acid monohydrate

Sodium citrate dihydrate

Sucrose

Polysorbate 80

Shelf Life

The expiry date is indicated on the packaging.

Storage

The storage conditions are detailed on the packaging.

Unopened vials

Do not freeze.

Protect from light. Store in the original carton until use.

Reconstituted solution

After reconstitution with Water for Injections, and dilution in 0.9% sodium chloride (normal saline), 0.45% sodium chloride (half normal saline), or Lactated Ringer's solution, the product is stable for up to 8 hours at 2°C to 8°C or at room temperature. Protect from direct sunlight.

Nature and Contents of Container

5 mL Type 1 glass vial sealed with a siliconised rubber stopper and a flip-off seal containing 120 mg *BENLYSTA* as a lyophylised powder.

20 mL Type 1 glass vial sealed with a siliconised rubber stopper and a flip-off seal containing 400 mg *BENLYSTA* as a lyophylised powder.

The drug is supplied in a single use vial without a preservative.

Incompatibilities

BENLYSTA is not compatible with 5% dextrose.

BENLYSTA must be prepared and administered only as directed, see *Use and Handling*.

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 to15 minutes for the vial to warm to room temperature.

It is recommended that a 21-25 gauge needle be used when piercing the vial stopper for reconstitution and dilution.

The 120 mg single-use vial of *BENLYSTA* should be 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* should be 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 minimise 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 five 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 direct 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 colourless 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% sodium chloride (normal saline), 0.45% sodium chloride (half normal saline) or Lactated Ringer’s solution for intravenous infusion. For patients whose body weight is less than or equal to 40 kg, infusion bags with 100 mL normal saline, half normal saline or Lactated Ringer’s solution may be considered providing that the resulting belimumab concentration in the infusion bag does not exceed 4 mg/mL.

5% Dextrose intravenous solutions are incompatible with *BENLYSTA* and should not be used.

From a 250 mL (or 100 mL) infusion bag or bottle of normal saline, half normal saline, or Lactated Ringer's solution, 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°C to 8°C. Solutions diluted in normal saline, half normal saline, or Lactated Ringer's solution may be stored at 2°C to 8°C or room temperature.

The total time from reconstitution of *BENLYSTA* to completion of infusion should not Exceed eight hours.

Administration

BENLYSTA should be 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.

Not all presentations are available in every country.

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