AUSTRALIAN PRODUCT INFORMATION

BENLYSTA (belimumab) powder for injection

BENLYSTA (belimumab) solution for injection

1 NAME OF THE MEDICINE

Belimumab (rmc).

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Belimumab is a 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.

Powder for intravenous infusion

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.

Solution for subcutaneous injection

Each pre-filled syringe or auto-injector delivers 200 mg belimumab in 1 mL (200 mg/mL).

List of excipients with known effect

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

Powder for intravenous infusion

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

Solution for subcutaneous injection

A clear to opalescent, colourless to pale yellow solution in a single-use, pre-filled syringe or auto-injector.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC 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.

4.2 DOSE AND METHOD OF ADMINISTRATION

Powder for intravenous infusion

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 Method of administration).

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 Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Patients should be monitored during and for an appropriate period of time after administration of BENLYSTA (See Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

There is limited data to support the benefit or durability of treatment beyond 52 weeks (See Section 5.1 PHARMACODYNAMIC PROPERTIES - 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 Section 5.1 PHARMACODYNAMIC PROPERTIES - Clinical trials).

Solution for subcutaneous injection

Pre-filled syringes or auto-injectors must NOT be used for intravenous injection.

It is recommended that the first subcutaneous injection of BENLYSTA should be under the supervision of a healthcare professional. The healthcare professional must provide proper training in subcutaneous technique and education about signs and symptoms of hypersensitivity reactions (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). A patient may self-inject or the patient's caregiver may administer BENLYSTA after the healthcare professional determines that it is appropriate (see enclosed Instructions for Use).

BENLYSTA may be given as a subcutaneous injection in the abdomen or thigh. When injecting in the same region, patients should be advised to use a different injection site each week; never give injections into areas where the skin is tender, bruised, red, or hard.

If a dose is missed, it should be administered as soon as possible. Thereafter, patients can resume dosing on their usual day of administration or start a new weekly schedule from the day that the missed dose was administered. It is not necessary to administer two doses on the same day.

If a patient is being transitioned from BENLYSTA intravenous therapy to BENLYSTA subcutaneous therapy, administer the first subcutaneous dose 1 to 4 weeks after the last intravenous dose (see Section 5.2 PHARMACOKINETIC PROPERTIES).

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 Section 5.1 PHARMACODYNAMIC PROPERTIES - Clinical trials).

Adults

The recommended dosage is 200 mg once weekly given as a subcutaneous injection in the abdomen or thigh, preferably on the same day each week.

Powder for intravenous infusion and solution for subcutaneous injection

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 Section 5.2 PHARMACOKINETIC PROPERTIES – 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 Section 5.2 PHARMACOKINETIC PROPERTIES – 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 Section 5.2 PHARMACOKINETIC PROPERTIES – Special patient populations).

Method of administration

Powder for intravenous infusion

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.

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 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 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 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, 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 2-8°C. Solutions diluted in normal saline, half normal saline, or Lactated Ringer's solution 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.

Solution for subcutaneous injection

BENLYSTA does not contain a preservative and is for single use in one patient only. The pre-filled syringe and auto-injector should be used once only and then discarded.

4.3 CONTRAINDICATIONS

BENLYSTA is contraindicated in patients who have demonstrated anaphylaxis to belimumab or to any of the excipients (See Section 2 QUALITATIVE AND QUANTITATIVE COMPOSITION).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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 or injection-related systemic reactions and hypersensitivity

As with all protein products, administration of BENLYSTA may result in infusion or injection-related systemic and hypersensitivity reactions, which can be severe, or fatal. In the event of a severe reaction, BENLYSTA administration must be interrupted and appropriate medical therapy administered (See Section 4.2 DOSE AND METHOD OF ADMINISTRATION). Patients with a history of multiple drug allergies or significant hypersensitivity may be at increased risk (See Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

In clinical trials, serious infusion and hypersensitivity reactions affected less than 1% of patients, and included anaphylactic reaction, bradycardia, hypotension, angioedema, and dyspnoea. Infusion or injection-related systemic and hypersensitivity reactions occurred more frequently with the first two doses and tended to decrease with subsequent doses. Delay in the onset of acute hypersensitivity reactions has been observed. 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. Delayed-type, non-acute hypersensitivity reactions may also occur and include symptoms such as rash, nausea, fatigue, myalgia, headache and facial oedema.

Serious infections

As with other immunomodulating agents, the mechanism of action of BENLYSTA may increase the risk for the development of infections. Severe infections, including fatal cases, have been reported in SLE patients receiving immunosuppressant therapy, including BENLYSTA (See Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). 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.

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.

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. 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 BENLYSTA 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.

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 and suicidality

In controlled clinical intravenous and subcutaneous studies, psychiatric disorders (depression, suicidal ideation and behaviour) have been reported [see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)]. Physicians should carefully assess the risk of depression and suicide considering the patient's medical history and current psychiatric status before treatment with belimumab, and continue to monitor patients during treatment. Physicians should advise patients (and caregivers where appropriate) to contact their healthcare professional about new or worsening psychiatric symptoms. The risk and benefit of continued treatment with belimumab should be carefully assessed for patients who develop such symptoms.

Mortality

There were more deaths reported with BENLYSTA than with placebo during the controlled period of the intravenous 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. Aetiologies included infection, cardiovascular disease and suicide.

In the controlled trial of BENLYSTA administered subcutaneously (N = 836), a total of 5 deaths occurred during the placebo-controlled, double-blind treatment period (0.7% [2/280] of patients receiving placebo and 0.5% [3/556] of patients receiving BENLYSTA). Infection was the most common cause of death.

The physicians should discuss this imbalance with their patients prior to initiating therapy.

Use in 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

Use in 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 (≥ 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.

Use in the elderly

No substantial differences were seen in safety and efficacy related to age (See Section 4.2 DOSE AND METHOD OF ADMINISTRATION). However, there is insufficient experience in this age group to draw firm conclusions.

Paediatric use

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

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No *in vivo* interaction studies have been performed. The formation of some CYP450 enzymes is suppressed by increased levels of certain cytokines during chronic inflammation. It is not known if belimumab could be an indirect modulator of such cytokines. A risk for indirect reduction of CYP activity by belimumab cannot be excluded. On initiation or discontinuation of belimumab, therapeutic monitoring should be considered for patients being treated with CYP substrates with a narrow therapeutic index, where the dose is individually adjusted (e.g. warfarin)..

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.

4.6 FERTILITY, PREGNANCY AND LACTATION

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

(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. Foetal deaths were observed in l4%, 24% and 15% of pregnant females monkeys in the 0, 5 and 150 mg/kg groups, respectively. Infant deaths occurred with an incidence of 0%, 8% and 5%. The cause of foetal 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.

If a woman treated with BENLYSTA gives birth to a child, 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 Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Use in lactation

The safety of BENLYSTA for use during lactation has not been established. 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.

It is recommended that a decision should be made about BENLYSTA therapy in breast-feeding mothers, taking into account the benefit of breast feeding for the child and the benefit of therapy for the mother, and any potential adverse effects on the breastfed child from BENLYSTA or from the underlying maternal condition.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Summary of safety profile

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

The data described below reflect exposure to BENLYSTA (10 mg/kg intravenously over a 1-hour period on Days 0, 14, 28, and then every 28 days up to 52 weeks) in 674 patients with SLE, including 472 exposed for up to 52 weeks and 556 patients exposed to 200 mg belimumab subcutaneously once weekly up to 52 weeks. The safety data presented include data beyond Week 52 in some patients. 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.

The following have been observed with BENLYSTA and are discussed in detail in Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE:

- Mortality
- Serious infections
- Infusion or injection-related systemic reactions and hypersensitivity
- PML
- Depression
- Malignancy

Adverse reactions were reported in the majority of BENLYSTA-treated and placebo-treated patients. The most frequently reported adverse reactions (≥ 5% of patients with SLE treated with BENLYSTA plus standard of care and at a rate ≥ 1% greater than placebo) were viral upper respiratory tract infections, bronchitis, and diarrhoea. The proportion of patients who discontinued treatment due to adverse reactions was 7% for BENLYSTA-treated patients and 8% for placebo-treated patients

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	Bacterial Infections e.g bronchitis, unrinary tract infection

System Organ Class	Frequency	Adverse Reaction(s)
	Common	Gastroenteritis viral, pharyngitis, nasopharyngitis, viral upper respiratory tract infection
Blood and lymphatic system disorders	Common	Leucopenia
Immune System Disorders	Common	Hypersensitivity reactions*
	Uncommon	Anaphylactic reaction, angioedema
	Rare	Delayed-type, non-acute hypersensitivity reaction
Psychiatric disorders	Common	Depression
	Uncommon	Suicidal ideation Suicidal behaviour
Nervous system disorders	Common	Migraine
Gastrointestinal disorders	Very common	Diarrhoea, nausea
Skin and Subcutaneous Tissue Disorders	Common	Injection site reactions**
	Uncommon	Rash Urticaria
Musculoskeletal and connective tissue disorders	Common	Pain in extremity
General Disorders and Administration Site Conditions	Common	Pyrexia, infusion or injection-related systemic reactions*

* 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 or injection-related systemic reactions' 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 or injection-related systemic reactions in all cases.

** Applies to subcutaneous formulation only.

Description of selected adverse reactions

Infusion or injection-related systemic reactions and hypersensitivity: Infusion or injection-related systemic reactions and hypersensitivity were generally observed on the day of administration, but acute hypersensitivity reactions may also occur several days after dosing. Patients with a history of multiple drug allergies or significant hypersensitivity reactions may be at increased risk.

The incidence of infusion reactions and hypersensitivity reactions after intravenous administration occurring within 3 days of an infusion was 12% in the group receiving BENLYSTA and 10% in the group receiving placebo, with 1.2% and 0.3%, respectively, requiring permanent treatment discontinuation.

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. Delayed-type, non-acute hypersensitivity reactions have also been observed and included symptoms such as rash, nausea, fatigue, myalgia, headache, and facial oedema.

The incidence of post-injection systemic reactions and hypersensitivity reactions occurring within 3 days of subcutaneous administration was 7% in the group receiving BENLYSTA and 9% in the group receiving placebo. Clinically significant hypersensitivity reactions associated with BENLYSTA administered subcutaneously and requiring permanent treatment discontinuation were reported in 0.2% of patients and in no patients receiving placebo.

Infections: In the intravenous 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; serious opportunistic infections accounted for < 1% and 0% of these, respectively. Some infections were severe or fatal.

In the subcutaneous clinical study, the overall incidence of infections was 55% in the group receiving BENLYSTA and 57% in the group receiving placebo. Only bacterial urinary tract infection occurred in at least 3% of patients receiving BENLYSTA and at least 1% more frequently than patients receiving placebo. Serious infections occurred in 4% of patients receiving BENLYSTA and 5% of patients receiving placebo; serious opportunistic infections accounted for 0.2% and 0% of these, respectively. Some infections were severe or fatal.

Injection site reactions: In the subcutaneous clinical study, the frequency of injection site reactions was 6.1% (34/556) and 2.5% (7/280) for patients receiving BENLYSTA and placebo, respectively. These injection site reactions (most commonly pain, erythema, hematoma, pruritus, and induration) were mild to moderate in severity. The majority did not necessitate drug discontinuation.

Adverse events

The most common (>10% in any treatment group) adverse events by MedRA preferred term reported in the intravenous studies are shown in Table 1 below.

Table 1: Most common (>10% in any treatment group) adverse events in intravenous studies.

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%)

Preferred Term	Placebo N = 675	BENLYSTA N = 674
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 BENLYSTA 10 mg/kg (intravenous administration)plus standard of care and at least 1% more frequently than in patients receiving placebo plus standard of care in 3 controlled SLE studies are shown in Table 2 below**.**

Table 2: Adverse events occurring in at least 3% of patients treated with BENLYSTA 10 mg/kg (intravenous administration)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

The adverse event summary for BENLYSTA intravenous administration and subcutaneous administration compared to placebo treated patients is shown in Table 3 below. The adverse event profile was consistent between the different routes of administration.

Table 3: Adverse event (AE) summary for BENLYSTA IV and SC compared to placebo treated patients.

Subjects with at least one	Number (%) of Subjects					
	C1056/C1057/LBSL02 Pooled IV		BEL112341-SC		Pooled IV + SC	
	Placebo IV (N=675)	BENLYSTA IV (N=1458)	PLACEBO SC (N=280)	BENLYSTA SC 200 mg (N=556)	Placebo IV+ Placebo SC (N=955)	BENLYSTA IV + BENLYSTA SC 200 mg (N=2014)
AE	623 (92.3%)	1354 (92.9%)	236 (84.3%)	449 (80.8%)	859 (89.9%)	1803 (89.5%)
Related AE	282 (41,8%)	586 (40.2%)	73 (26.1%)	173 (31.1%)	355 (37.2%)	759 (37.7%)
Serious AE	103 (15.3%)	248 (17.0%)	44 (15.7%)	60 (10.8%)	147 (15.4%)	308 (15.3%)
Severe[a] AE	99 (14.7%)	220 (15.1%)	40 (14.3%)	55 (9.9%)	139 (14.6%)	275 (13.7%)
Serious and/or severe[a] AE	138 (20.4%)	328 (22.5%)	59 (21.1%)	82 (14.7%)	197 (20.6%)	410 (20.4%)
AE resulting in study agent discontinuation	48 (7.1%)	88 (6.0%)	25 (8.9%)	40 (7.2%)	73 (7.6%)	128 (6.4%)
Death	3 (0.4%)	11 (0.8%)	2 (0.7%)	3 (0.5%)	5 (0.5%)	14 (0.7%)

[a] Severe or life threatening

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

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

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

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 and neutralising 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

Powder for intravenous infusion

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 C3 and C4 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.

Study BEL112233, a long-term uncontrolled extension study of BLISS-76 (See *CLINICAL TRIALS*), enrolled 268 patients. B cells and IgG levels were followed for 7 years or longer with ongoing belimumab treatment in varying numbers (n) of subjects depending on the pharmacodynamic measure. Sustained decreases relative to baseline levels of BLISS-76 in various B cell subsets were observed leading to median reductions of 87% in naive B cells (n=107), 67% in memory B cells (n=106), 99% in activated B cells (n=116), and 92% in plasma cells (n=118) after more than 7 years of treatment. After about 7 years, a 28% median reduction in IgG levels (n=150) was observed. Throughout the period of follow-up, 8 out of

268 participants (3.0%) recorded IgG levels below 400 mg/dL and 1.6% (2/129) recorded a decrease in IgG levels to below 400 mg/dL in the 7th year. Over the course of the study, the reported incidence of AEs generally remained stable or declined.

Solution for subcutaneous injection

Reductions in elevated levels of serum IgG and in anti-dsDNA antibodies were observed as early as week 8 and week 4, respectively, and continued to week 52. Median IgG levels at week 52 were reduced by 11% in patients receiving belimumab compared with an increase of 0.7% in patients receiving placebo. In patients with anti-dsDNA antibodies at baseline, median anti-dsDNA antibodies levels at week 52 were reduced by 56% in patients receiving belimumab compared with 41% in patients receiving placebo. In patients with anti-dsDNA antibodies at baseline, by week 52, 18% of patients treated with belimumab had converted to anti-dsDNA negative compared with 15% of the patients receiving placebo.

In patients with low complement levels at baseline, belimumab treatment resulted in increases in complement C3 and C4 which were seen as early as week 12, and continued to week 52. By week 52, levels of C3 and C4 had normalised in 42% and 53% of patients receiving belimumab compared with 21% and 20% 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, transitional, naïve, plasma, and the SLE B cell subset at week 52. Reductions in naïve and transitional B 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 with belimumab administered intravenously, 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 intravenously. However, the presence of anti-belimumab antibodies was relatively uncommon in patients with belimumab administered intravenously, 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.

Serum samples from more than 550 patients with SLE were tested; no anti-belimumab antibodies were detected during or after treatment with belimumab 200 mg administered subcutaneously.

Clinical trials

Powder for intravenous infusion

Phase II Study

The efficacy of belimumab administered intravenously 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 (≤ 9 vs ≥10), proteinuria level (<2 g per 24 hr vs ≥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:

- ≥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 4.

Table 4: 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 5.

Table 5: 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 19.8 (p<0.0001)
SRI response rate (excluding complement and anti-dsDNA changes) at Week 52 (%) Observed treatment difference vs placebo (%)	28.9	46.2 17.3 (p<0.0001)
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 6.3 (p=0.0964)
FACIT-fatigue score improvement from baseline at Week-52 (mean) Observed treatment difference vs placebo (mean difference)	1.99	4.21 2.21 (p=0.0048)
BLISS-76 Study only	Placebo (n=131)	Benlysta 10 mg/kg (n=134)

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-76 (%)	27.5	39.6
Observed treatment difference vs placebo (%)		12.1 (p=0.0160)

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

Solution for subcutaneous injection

The efficacy of belimumab administered subcutaneously was evaluated in a randomised, double blind, placebo controlled, 52-week Phase III study (HGS1006-C1115; BEL112341) in 836 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 greater than or equal to 8 and positive anti-nuclear antibody (ANA or anti-dsDNA) test results (ANA titre greater than or equal to 1:80 and/or anti-dsDNA greater than or equal to 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, non-steroidal anti-inflammatory medications or other immunosuppressives. Patients were excluded from the study if they had severe active central nervous system lupus or severe active lupus nephritis, if they had received another biological investigational agent in the previous 3 months, or if they had a positive response to testing for HIV antibody, hepatitis B surface antigen, or hepatitis C antibody.

This study was conducted in the US, South America, Europe and Asia. Patient median age was 37 years (range: 18 to 77 years), and the majority (94%) were female. Patients were randomised in a 2:1 ratio to receive belimumab 200 mg or placebo subcutaneously once weekly for 52 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.

Secondary efficacy endpoints included time to first severe flare (as measured by the modified SELENA-SLEDAI SLE Flare Index) and the proportion of patients whose average prednisone

dose has been reduced by ≥25% from baseline to ≤7.5 mg/day during Weeks 40 through 52. A health outcomes endpoint included mean change in the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Scale score at Week 52.

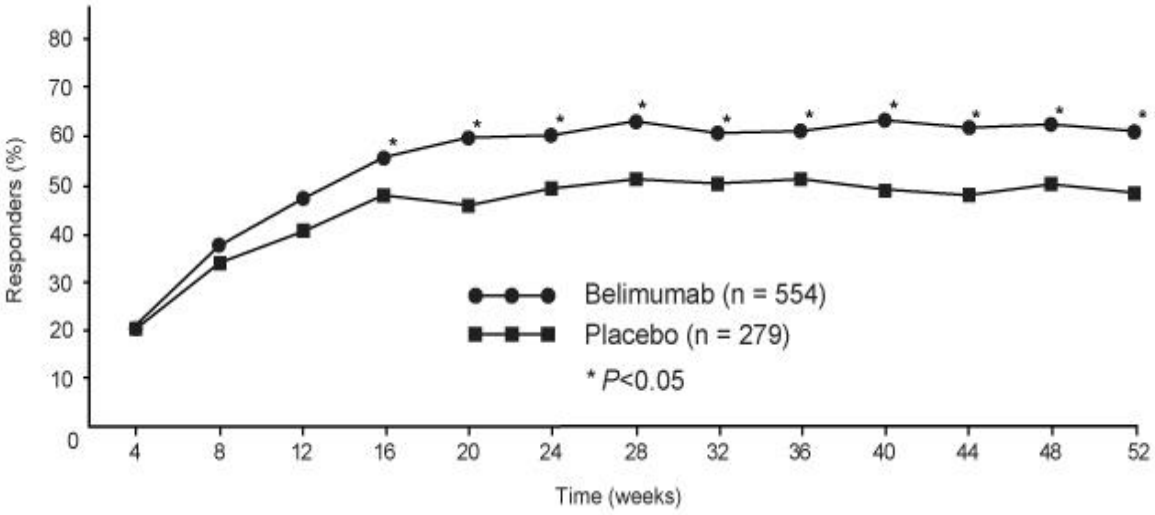
Belimumab produced significant improvements in the SLE Responder Index as well as in the individual component SELENA SLEDAI score, see Table 6.

Table 6: Response Rate at Week 52

Response	**Placebo** **(n=279)**	**Belimumab** **200 mg SC weekly** **(n=554)**
SLE Responder Index Observed difference vs placebo Odds ratio (95%CI) vs placebo	48.4%	61.4% 12.98% (p=0.0006) 1.68 (1.25, 2.25)
Components of SLE Responder Index		
Percent of patients with reduction in SELENA-SLEDAI ≥4 Observed difference vs placebo	49.1%	62.3% 13.17% (p=0.0005)
Percent of patients with no worsening by BILAG index Observed difference vs placebo	74.2%	80.9% 6.67% (p=0.0305)
Percent of patients with no worsening by PGA Observed difference vs placebo	72.8%	81.2% 8.47% (p=0.0061)

The differences between the treatment groups were apparent by week 16 and sustained through week 52 (Figure 1).

Figure 1. Proportion of SRI Responders by Visit



A severe flare in SLE was defined by the modified SELENA SLEDAI SLE Flare Index where the modification excludes severe flares that are triggered only by an increase of the SELENA SLEDAI score to greater than 12. The risk of severe flares was reduced by 49% during the 52 weeks of observation in the group receiving belimumab compared with the group receiving placebo (hazard ratio=0.51; P=0.0004). Of the patients experiencing a severe flare, the median time to the first severe flare was delayed in patient receiving belimumab compared with placebo (171 days vs. 118 days).

At baseline, 60% of patients were receiving prednisone at doses >7.5 mg/day (or equivalent). Among these patients, 18.2% of patients receiving belimumab reduced their average prednisone dose by at least 25% to ≤7.5 mg/day during weeks 40 through 52 compared to 11.9% of patients on placebo. However, the difference was not statistically significant (P=0.0732).

Belimumab demonstrated improvement in fatigue compared with placebo as measured by the FACIT Fatigue Scale score. The mean improvement in FACIT-Fatigue Scale score from baseline to week 52 was significantly greater with belimumab (4.4) compared with placebo (2.7); (P=0.0130). Among patients receiving belimumab, 44.4% of patients experienced improvement in FACIT-Fatigue Scale score exceeding the minimally important clinical difference (improvement greater than or equal to 4) at week 52 compared with 36.1% of patients receiving placebo (P=0.0245).

Subgroup analysis of the primary endpoint demonstrated that the greatest benefit was observed in patients with higher disease activity at baseline, 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.

An additional, previously identified serologically active group, those patients with low complement and positive anti-dsDNA at baseline, also demonstrated a greater relative response, see Table 7 for results of this example of a higher disease activity group.

Table 7: Patients with low complement and positive anti-dsDNA at baseline

Subgroup	Anti-dsDNA positive AND low complement	
	Placebo	Belimumab 200 mg SC weekly
	(n=108)	(n=246)
SRI response rate at Week 52 (%)	47.2	64.6
Observed treatment difference vs placebo (%)		17.41 (p=0.0014)
Severe flares over 52 weeks:	(n=108)	(n=248)
Patients experiencing a severe flare (%)	31.5	14.1
Observed treatment difference vs placebo (%)		17.4
Time to severe flare [Hazard ratio (95% CI)]		0.38 (0.24, 0.61) (p<0.0001)
	(n=70)	(n=164)
Prednisone reduction by ≥25% from baseline to ≤7.5 mg/day during Weeks 40 through 52 (%)	11.4	20.7
Observed treatment difference vs placebo (%)		9.3 (p=0.0844)
	(n=108)	(n=248)
FACIT-fatigue score improvement from baseline at Week-52 (mean):	2.4	4.6
Observed treatment difference vs placebo		2.1 (p=0.0324)

5.2 PHARMACOKINETIC PROPERTIES

The intravenous 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 from 563 patients who received belimumab 10 mg/kg intravenously in the two Phase III studies.

The subcutaneous pharmacokinetic parameters below are based on population parameter estimates from 661 subjects, comprised of 554 SLE patients and 107 healthy subjects, who received belimumab subcutaneously.

Absorption

Following intravenous administration, maximum serum concentrations (Cmax) of belimumab were generally observed at, or shortly after, the end of the infusion. The Cmax was 311 (231–448) µg/mL at steady-state based on simulating the concentration time profile using the typical parameter values of the population pharmacokinetic model.

Following subcutaneous administration, the maximum serum concentration (Cmax) of belimumab at steady state was 108 µg/mL and the time to reach steady-state Cmax after administration (Tmax) was 2.6 days. The bioavailability of belimumab was approximately 74%.

Distribution

Belimumab was 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.

Excretion

Following intravenous administration, 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.

Following subcutaneous administration, belimumab had a terminal half-life of 18.3 days. The distribution half-life was 1.1 days. For subcutaneous administration, the biphasic decline observed with intravenous belimumab was masked by the slow absorption phase. The systemic clearance was 204 mL/day.

Transitioning from Intravenous to Subcutaneous Administration

SLE patients transitioning from 10 mg/kg intravenously every 4 weeks to 200 mg subcutaneously weekly using a 1 to 4 week switching interval had pre-dose belimumab serum concentrations at their first subcutaneous dose close to their eventual subcutaneous steady-state trough concentration (see section 4.2 DOSE AND METHOD OF ADMINISTRATION). Based on simulations with population PK parameters the steady-state average belimumab concentrations for 200 mg subcutaneous every week were similar to 10 mg/kg intravenous every 4 weeks.

Special Patient Populations

The following information is based on the population pharmacokinetic analysis.

Elderly

Belimumab has been studied in a limited number of elderly patients. Age did not affect belimumab exposure in the intravenous and subcutaneous 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 administered intravenously and subcutaneously 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). Following belimumab administered intravenously, proteinuria (≥ 2 g/day) increased belimumab clearance, and decreases in creatinine clearance decreased belimumab clearance. Similar effects were observed but were not statistically significant for belimumab administered subcutaneously. These effects were within the expected range of variability for belimumab administered intravenously and subcutaneously. 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 administered intravenously or subcutaneously. The effects of body size on belimumab exposure after intravenous administration are accounted for by weight normalised dosing. The effects of body weight and BMI on belimumab exposure after subcutaneous administration were not considered clinically meaningful. There was no significant impact on efficacy or safety based on weight. Therefore, no dose adjustment is recommended.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

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

Carcinogenicity

The carcinogenic potential of BENLYSTA has not been investigated.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Powder for intravenous infusion

BENLYSTA also contains sodium citrate dihydrate, citric acid- monohydrate, sucrose and polysorbate 80.

Solution for subcutaneous injection

BENLYSTA also contains L-arginine hydrochloride, L-histidine, L-histidine monohydrochloride, polysorbate 80, sodium chloride and water for injections

6.2 INCOMPATIBILITIES

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.

6.3 SHELF LIFE

Powder for intravenous infusion

Unopened vials

60 months.

Solution for subcutaneous injection

36 months

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Powder for intravenous infusion

Unopened vials

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 0.9% sodium chloride (normal saline), half normal saline, or Lactated Ringer's solution and stored at 2° to 8°C or room temperature. Any unused solution remaining after this time should be discarded.

Solution for subcutaneous injection

Store at 2°C to 8°C (Refrigerate. Do not freeze.)

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

6.5 NATURE AND CONTENTS OF CONTAINER

Powder for intravenous infusion

BENLYSTA is supplied as a lyophilised 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.

Solution for subcutaneous injection

Pre-filled pen (autoinjector) (single dose)

1 mL siliconised, USP Type I glass syringe with 13mm, 27G, stainless steel needle assembled as an auto-injector.

Pre-filled syringe (single dose)

1 mL siliconised, USP Type I glass syringe with 13mm, 27G, stainless steel needle assembled with a needle guard.

Available in packs of 1 or 4 pre-filled pens or syringes

Each pre-filled syringe and pre-filled pen delivers 200 mg belimumab in 1 mL.

Not all pack sizes may be distributed in Australia.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

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

Belimumab has a pH of 6.5.

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

CAS number

356547-88-1

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8 SPONSOR

GlaxoSmithKline Australia Pty Ltd

Level 4, 436 Johnston Street,

Abbotsford, Victoria, 3067

9 DATE OF FIRST APPROVAL

19 October 2012

10 DATE OF REVISION

27 November 2019

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
2	Solution for injection quantitative composition
3	Solution for injection pharmaceutical form
4.2	Solution for injection dosing information
4.8	Solution for injection adverse event information
5.1	Solution for injection pharmacodynamic and clinical trial data
5.2	Solution for injection pharmacokinetic data
6.0	Solution for injection excipient information
6.3	Solution for injection shelf life information
6.4	Solution for injection storage information
6.5	Solution for injection nature and contents information

Version 11.0