ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Benlysta 200 mg solution for injection in pre-filled pen.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 mL pre-filled pen contains 200 mg of belimumab.

Belimumab is a human, IgG1λ monoclonal antibody, produced in a mammalian cell line (NS0) by recombinant DNA technology.

Excipient with known effect

Each pre-filled pen contains 0.1 mg polysorbate 80.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in pre-filled pen (injection)

A clear to opalescent, colourless to pale yellow solution, with a pH of 6 and an osmolality of 270 – 320 mOsm/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Benlysta is indicated as add-on therapy in patients aged 5 years and older with active, autoantibody-positive systemic lupus erythematosus (SLE) with a high degree of disease activity (e.g., positive anti-dsDNA and low complement) despite standard therapy (see section 5.1).

Benlysta is indicated in combination with background immunosuppressive therapies for the treatment of adult patients with active lupus nephritis (see sections 4.2 and 5.1).

4.2 Posology and method of administration

Benlysta treatment should be initiated and supervised by a qualified physician experienced in the diagnosis and treatment of SLE. It is recommended that the first subcutaneous injection of Benlysta is given under the supervision of a healthcare professional in a setting that is sufficiently qualified to manage hypersensitivity reactions, if necessary. The healthcare professional must provide proper training in subcutaneous technique and education about signs and symptoms of hypersensitivity reactions (see section 4.4). A patient may self-inject, or the patient caregiver may administer Benlysta after the healthcare professional determines that it is appropriate.

For patients under 10 years of age, Benlysta pre-filled pen must be administered by a healthcare professional or trained caregiver.

Posology

SLE

The patient's condition should be evaluated continuously. Discontinuation of treatment with Benlysta is to be considered if there is no improvement in disease control after 6 months of treatment.

Adults
The recommended dose is 200 mg once weekly, administered subcutaneously. Dosing is not based on weight (see section 5.2).

Children and adolescents (aged 5 to less than 18 years)
The recommended subcutaneous dose is based on weight (see sections 5.1 and 5.2).

Body weight	Recommended dose
≥ 50 kg	200 mg once weekly
30 to < 50 kg	200 mg every 10 days
15 to < 30 kg	200 mg every 2 weeks

Lupus nephritis

Adults
In patients initiating therapy with Benlysta for active lupus nephritis, the recommended dosage regimen is a 400 mg dose (two 200 mg injections) once weekly for 4 doses, then 200 mg once weekly thereafter. In patients continuing therapy with Benlysta for active lupus nephritis, the recommended dosage is 200 mg once weekly. Benlysta is to be used in combination with corticosteroids and mycophenolate or cyclophosphamide for induction, or mycophenolate or azathioprine for maintenance. The patient's condition should be evaluated continuously.

Missed doses

If a dose is missed, it is recommended to be administered as soon as possible. Thereafter, patients can resume dosing on their usual day of administration, or start a new schedule from the day that the missed dose was administered.

Changing the scheduled dosing day

If patients wish to change their scheduled dosing day, a new dose can be given on the newly preferred day of the week. Thereafter the patient can continue with the new schedule from that day, even if the dosing interval may be temporarily less than usual.

Transition from intravenous to subcutaneous administration

SLE
If a patient with SLE is being transitioned from Benlysta intravenous administration to subcutaneous administration, the first subcutaneous injection must be administered 1 to 4 weeks after the last intravenous dose (see section 5.2).

Lupus nephritis
If a patient with lupus nephritis is being transitioned from Benlysta intravenous administration to subcutaneous administration, it is recommended that the first dose of 200 mg subcutaneous injection be administered 1 to 2 weeks after the last intravenous dose. This transition can occur any time after the patient completes the first 2 intravenous doses (see section 5.2).

Special populations

Elderly

Data on patients ≥ 65 years are limited (see section 5.1). Benlysta should be used with caution in the elderly. Dose adjustment is not required (see section 5.2).

Renal impairment

Belimumab has been studied in a limited number of SLE patients with renal impairment. On the basis of the available information, dose 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 lack of data (see section 5.2).

Hepatic impairment

No specific studies with Benlysta have been conducted in patients with hepatic impairment. Patients with hepatic impairment are unlikely to require dose adjustment (see section 5.2).

Paediatric population

SLE
The safety and efficacy of Benlysta subcutaneous administration in children under 5 years of age or less than 15 kg have not been established. No data are available.

Lupus nephritis
The safety and efficacy of Benlysta subcutaneous administration in children and adolescents under 18 years of age have not been established. No data are available.

Method of administration

The pre-filled pen must be used for subcutaneous injection only. The recommended injection sites are the abdomen or thigh. When injecting in the same region, patients must be advised to use a different injection site for each injection; injections must not be given into areas where the skin is tender, bruised, red, or hard. When a 400 mg dose is administered at the same site, it is recommended that the 2 individual 200 mg injections are administered at least 5 cm (approximately 2 inches) apart.

Comprehensive instructions for subcutaneous administration of Benlysta in a pre-filled pen are provided at the end of the package leaflet (see Step-by-step instructions).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

In order to improve traceability of biological medicinal products, the tradename and the batch number of the administered product should be clearly recorded.

Benlysta has not been studied in the following patient groups and is not recommended in:

- severe active central nervous system lupus
- 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

Available data do not support the co-administration of rituximab with Benlysta in patients with SLE (see section 5.1). Caution needs to be exercised if Benlysta is co-administered with other B cell targeted therapy.

Hypersensitivity

Administration of subcutaneous or intravenous Benlysta may result in hypersensitivity reactions which can be severe, and fatal. In the event of a severe reaction, Benlysta administration must be interrupted and appropriate medical therapy administered (see section 4.2). The risk of hypersensitivity reactions is greatest with the first two doses; however, the risk must be considered for every administration. Patients with a history of multiple drug allergies or significant hypersensitivity may be at increased risk. Recurrence of clinically significant reactions after initial appropriate treatment of symptoms has also been observed (see sections 4.2 and 4.8).

Patients must be advised that hypersensitivity reactions are possible, on the day of, or several days after administration, and be informed of potential signs and symptoms and the possibility of recurrence. Patients must be instructed to seek immediate medical attention if they experience any of these symptoms. The package leaflet must be available to the patient. Delayed-type, non-acute hypersensitivity reactions have also been observed and included symptoms such as rash, nausea, fatigue, myalgia, headache, and facial oedema.

In intravenous clinical studies, serious infusion and hypersensitivity reactions included anaphylactic reaction, bradycardia, hypotension, angioedema, and dyspnoea. Please refer to the Summary of Product Characteristics for Benlysta powder for concentrate for solution for infusion (section 4.4).

Infections

The mechanism of action of belimumab could increase the risk for the development of infections in adults and children with lupus, including opportunistic infections, and younger children may be at increased risk. In controlled clinical studies, the incidence of serious infections was similar across the Benlysta and placebo groups; however, fatal infections (e.g. pneumonia and sepsis) occurred more frequently in patients receiving Benlysta compared with placebo (see section 4.8). Pneumococcal vaccination should be considered before initiating Benlysta treatment. Benlysta must not be initiated in patients with active serious infections (including serious chronic infections). Physicians need to exercise caution and carefully assess if the benefits are expected to outweigh the risks when considering the use of Benlysta in patients with a history of recurrent infection. Physicians need to advise patients to contact their health care provider if they develop symptoms of an infection. Patients who develop an infection while undergoing treatment with Benlysta must be monitored closely and careful consideration given to interrupting immunosuppressant therapy including Benlysta until the infection is resolved. The risk of using Benlysta in patients with active or latent tuberculosis is unknown.

Depression and suicidality

In controlled clinical intravenous and subcutaneous studies, psychiatric disorders (depression, suicidal ideation and behaviour including suicides) have been reported more frequently in patients receiving Benlysta (see section 4.8). Physicians should 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 must advise patients (and caregivers where appropriate) to contact their health care provider about new or worsening psychiatric symptoms. In patients who experience such symptoms, treatment discontinuation is to be considered.

Severe cutaneous adverse reactions

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), which can be life-threatening or fatal, have been reported in association with Benlysta treatment. Patients should be advised of the signs and symptoms of SJS and TEN and monitored closely for skin reactions. If signs and symptoms suggestive of these reactions appear, Benlysta should be withdrawn immediately, and an alternative treatment should be considered. If the patient has developed SJS or TEN with the use of Benlysta, treatment with Benlysta must not be restarted in this patient at any time.

Progressive multifocal leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) has been reported with Benlysta treatment for SLE. Physicians must be particularly alert to symptoms suggestive of PML that patients may not notice (e.g., cognitive, neurological or psychiatric symptoms or signs). Patients should be monitored for any of these new or worsening symptoms or signs, and if such symptoms/signs occur, referral to a neurologist and appropriate diagnostic measures for PML must be considered as clinically indicated. If PML is suspected, immunosuppressant therapy, including Benlysta, must be suspended until PML has been excluded. If PML is confirmed, immunosuppressant therapy, including Benlysta, must be discontinued.

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, belimumab may interfere with the response to immunisations. However, in a small 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 receiving standard immunosuppressive treatment at the time of vaccination. There are insufficient data to draw conclusions regarding response to other vaccines.

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. In a substudy, a small group of patients who had previously received either tetanus, pneumococcal or influenza vaccinations were found to maintain protective titres after treatment with Benlysta.

Malignancies and lymphoproliferative disorders

Immunomodulatory medicinal products, including Benlysta, may increase the risk of malignancy. Caution is advised when considering Benlysta therapy for patients with a history of malignancy or when considering continuing treatment in patients who develop malignancy. Patients with malignant neoplasm within the last 5 years have not been studied, with the exception of those with basal or squamous cell cancers of the skin, or cancer of the uterine cervix, that has been fully excised or adequately treated.

Polysorbate 80 content

This medicinal product contains polysorbate 80 (see section 2), which may cause allergic reactions.

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

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 is to be considered for patients being treated with CYP substrates with a narrow therapeutic index, where the dose is individually adjusted (e.g. warfarin).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

Women of childbearing potential must use effective contraception during Benlysta treatment and for at least 4 months after the last treatment.

Pregnancy

There are a limited amount of data from the use of Benlysta in pregnant women. Besides an expected pharmacological effect i.e. reduction of B cells, animal studies in monkeys do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). Benlysta should not be used during pregnancy unless the potential benefit justifies the potential risk to the foetus.

Breast-feeding

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 monkeys administered 150 mg/kg body weight every 2 weeks.

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

Fertility

There are no data on the effects of belimumab on human fertility. Effects on male and female fertility have not been formally evaluated in animal studies (see section 5.3).

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. No detrimental effects on such activities are predicted from the pharmacology of belimumab. It is recommended that the clinical status of the subject and the adverse reaction profile of Benlysta be borne in mind when considering the patient's ability to perform tasks that require judgement, motor or cognitive skills.

4.8 Undesirable effects

Summary of the safety profile

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

The data presented in the table below reflect exposure in 674 patients with SLE from the three pre-registration clinical studies and 470 patients in the subsequent placebo-controlled study administered Benlysta intravenously (10 mg/kg body weight over a 1-hour period on Days 0, 14, 28, and then every 28 days for up to 52 weeks), and 556 patients with SLE exposed to 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 body weight 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 medicinal products, anti-malarials, non-steroidal anti-inflammatory medicinal products.

Adverse reactions were reported in 84 % of Benlysta-treated patients and 87 % of placebo-treated patients. The most frequently reported adverse reaction (≥ 5 % of patients with SLE treated with Benlysta plus standard of care and at a rate ≥ 1 % greater than placebo) was nasopharyngitis. The proportion of patients who discontinued treatment due to adverse reactions was 7 % for Benlysta-treated patients and 8 % for placebo-treated patients.

The most frequently reported adverse reactions (> 5 % of patients with active lupus nephritis treated with Benlysta plus standard of care) were upper respiratory tract infection, urinary tract infection, and herpes zoster. The proportion of patients who discontinued treatment due to adverse reactions was 12.9 % for Benlysta-treated patients and 12.9 % for placebo-treated patients.

Severe cutaneous adverse reactions: Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported in association with Benlysta treatment (see section 4.4).

Tabulated list of adverse reactions

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

Very common	≥ 1/10
Common	≥ 1/100 to < 1/10
Uncommon	≥ 1/1000 to < 1/100
Rare	≥ 1/10 000 to < 1/1000
Not known	cannot be estimated from the available data.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. The frequency given is the highest seen with either formulation.

System organ class	Frequency	Adverse reactions
Infections and infestations[1]	Very common	Bacterial infections, e.g. bronchitis, urinary tract infection
	Common	Gastroenteritis viral, pharyngitis, nasopharyngitis, viral upper respiratory tract infection
Blood and lymphatic system disorders	Common	Leucopenia
Immune system disorders	Common	Hypersensitivity reactions[2]
	Uncommon	Anaphylactic reaction
	Rare	Delayed-type, non-acute hypersensitivity reactions
Psychiatric disorders	Common	Depression
	Uncommon	Suicidal behaviour, suicidal ideation
Nervous system disorders	Common	Migraine
Gastrointestinal disorders	Common	Diarrhoea, nausea
Skin and subcutaneous tissue disorders	Common	Injection site reactions[3], urticaria, rash
	Uncommon	Angioedema
	Not known	Stevens-Johnson syndrome, toxic epidermal necrolysis
Musculoskeletal and connective tissue disorders	Common	Pain in extremity
General disorders and administration site conditions	Common	Infusion or injection-related systemic reactions[2], pyrexia

[1] See 'Description of selected adverse reactions' and section 4.4 'Infections' for further information.
[2] '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.
[3] Applies to subcutaneous formulation only.

Description of selected adverse reactions

Data presented below are pooled from the three pre-registration intravenous clinical studies (10 mg/kg body weight intravenous dose only) and the subcutaneous clinical study. 'Infections' and 'Psychiatric disorders' also include data from a post-marketing study.

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.

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 receiving Benlysta and in no patients receiving placebo.

Infections: The overall incidence of infections in intravenous and subcutaneous pre-registration SLE studies was 63 % in both groups receiving Benlysta or placebo. Infections occurring in at least 3 % of patients receiving Benlysta and at least 1 % more frequently than patients receiving placebo were viral upper respiratory tract infection, bronchitis, and urinary tract infection bacterial. Serious infections occurred in 5 % of patients in both groups receiving Benlysta or placebo*;* serious opportunistic infections accounted for 0.4 % and 0 % of these, respectively. Infections leading to discontinuation of treatment occurred in 0.7 % of patients receiving Benlysta and 1.5 % of patients receiving placebo. Some infections were severe or fatal.

For information on infections observed in paediatric patients with SLE see Paediatric population section below.

In the lupus nephritis study, patients were receiving a background of standard therapy (see section 5.1) 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.

In a randomised, double-blind, 52-week, post-marketing safety SLE study (BEL115467) which assessed mortality and specific adverse events in adults, serious infections occurred in 3.7 % of patients receiving Benlysta (10 mg/kg body weight intravenously) vs. 4.1 % of patients receiving placebo. However, fatal infections (e.g. pneumonia and sepsis) occurred in 0.45 % (9/2002) of Benlysta-treated patients vs. 0.15 % (3/2001) of patients receiving placebo, while the incidence of all-cause mortality was 0.50 % (10/2002) vs. 0.40 % (8/2001), respectively. Most fatal infections were observed during the first 20 weeks of treatment with Benlysta.

Psychiatric disorders: In the pre-registration intravenous SLE clinical studies, serious psychiatric events were reported in 1.2 % (8/674) of patients receiving Benlysta 10 mg/kg body weight 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 body weight and 0.3 % (2/675) of patients receiving placebo. There were two suicides in Benlysta-treated patients (including one receiving Benlysta 1 mg/kg body weight).

In a 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) of patients receiving placebo. The overall incidence of serious suicidal ideation or behaviour or self-injury without suicidal intent was 0.7 % (15/2002) in patients receiving Benlysta and 0.2 % (5/2001) in the placebo group. No suicide was reported in either group.

The intravenous SLE studies above 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.

Leucopenia: The incidence of leucopenia reported in patients with SLE as an adverse event was 3 % in the group receiving Benlysta and 2 % in the group receiving placebo.

Injection site reactions: In the subcutaneous SLE 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.

Paediatric population

The adverse reaction profile in paediatric patients is based on one subcutaneous study and one intravenous study.

In a 52-week open-label study in which 25 paediatric patients (10 to 17 years of age) with SLE received subcutaneous Benlysta at a comparable exposure to adults (200 mg at a set dosing interval based on body weight, on a background of concomitant treatments), the safety profile in paediatric patients receiving Benlysta subcutaneously was consistent with the known safety profile for belimumab.

In a 52-week placebo-controlled study in which 53 patients (6 to 17 years of age) with SLE received Benlysta (10 mg/kg body weight intravenously on Days 0, 14, 28, and then every 28 days, on a background of concomitant treatments), no new safety signals were observed in the paediatric population 12 years of age and above (n = 43). Safety data in children younger than 12 years of age (n = 10) are limited.

Infections
5- to 11-year-old group: infections were reported in 8/10 patients receiving Benlysta intravenously and 3/3 patients receiving placebo, and serious infections were reported in 1/10 patients receiving Benlysta intravenously and 2/3 patients receiving placebo (see section 4.4).
12- to 17-year-old group: infections were reported in 22/43 patients receiving Benlysta intravenously and 25/37 patients receiving placebo, and serious infections were reported in 3/43 patients receiving Benlysta intravenously and 3/37 patients receiving placebo. In the open-label extension phase there was one fatal infection in a patient receiving Benlysta intravenously.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via the national reporting system listed in Appendix V.

4.9 Overdose

There is limited clinical experience with overdose 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 body weight 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 body weight.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, monoclonal antibodies, ATC code: L04AG04

Mechanism of action

Belimumab is a human IgG1λ monoclonal antibody specific for soluble human B Lymphocyte Stimulator protein (BLyS, also referred to as BAFF and TNFSF13B). Belimumab blocks the binding of soluble BLyS, a B cell survival factor, to its receptors on B cells. 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.

BLyS levels are elevated in patients with SLE and other autoimmune diseases. There is an association between plasma BLyS levels and SLE disease activity. The relative contribution of BLyS levels to the pathophysiology of SLE is not fully understood.

Pharmacodynamic effects

Median IgG levels at Week 52 were reduced by 11 % in patients with SLE receiving Benlysta 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 Benlysta compared with 41 % in patients receiving placebo. In patients with anti-dsDNA antibodies at baseline, by Week 52, 18 % of patients treated with Benlysta had converted to anti-dsDNA negative compared with 15 % of the patients receiving placebo.

In patients with SLE with low complement levels, normalization of C3 and C4 was observed by Week 52 in 42 % and 53 % of patients receiving Benlysta and in 21 % and 20 % of patients receiving placebo, respectively.

Benlysta significantly reduced circulating overall, transitional, naïve, and SLE B cells, as well as plasma cells 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.

The B cell and IgG response to long term treatment with intravenous Benlysta was assessed in an uncontrolled SLE extension study. After 7 and a half years of treatment (including the 72-week parent study), a substantial and sustained decrease in various B cell subsets was observed leading to 87 % median reduction in naïve B cells, 67 % in memory B cells, 99 % in activated B cells, and 92 % median reduction 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 Benlysta (10 mg/kg body weight intravenously) 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 Benlysta group as expected with the known mechanism of belimumab. At Week 104, the median percent increase from baseline in IgG was 17 % for Benlysta 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 one intravenous study in paediatric patients with SLE (6 to 17 years of age) and one subcutaneous study in paediatric patients with SLE (10 to 17 years of age), the pharmacodynamic response was consistent with the adult data.

Immunogenicity

In the subcutaneous study where serum samples from more than 550 adult patients with SLE were tested, no anti-belimumab antibodies were detected during or after treatment with belimumab 200 mg subcutaneously. In the lupus nephritis study where 224 adult patients received Benlysta 10 mg/kg body weight intravenously, no anti-belimumab antibodies were detected.

In one intravenous study in 6- to 17-year-old paediatric patients (n = 53) with SLE and one subcutaneous study in 10- to 17-year-old paediatric patients (n = 25) with SLE, none of the patients developed anti-belimumab antibodies.

Clinical efficacy and safety

SLE

Subcutaneous injection
The efficacy of Benlysta administered subcutaneously was evaluated in a randomised, double-blind, placebo-controlled 52-week Phase III study (HGS1006-C1115; BEL112341) in 836 adult 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 ≥ 8 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.

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. Background medicinal products included corticosteroids (86 %; > 7.5 mg/day prednisone equivalent 60 %), immunosuppressives (46 %), and anti-malarials (69 %). Patients were randomised in a 2:1 ratio to receive belimumab 200 mg or placebo subcutaneously once weekly for 52 weeks.

At baseline 62.2 % of patients had high disease activity (SELENA SLEDAI score ≥ 10), 88 % of patients had mucocutaneous, 78 % had musculoskeletal, 8 % had haematological, 12 % had renal, and 8 % had vascular organ involvement.

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 measures improvement in SLE disease activity, without worsening in any organ system, or in the patient's overall condition.

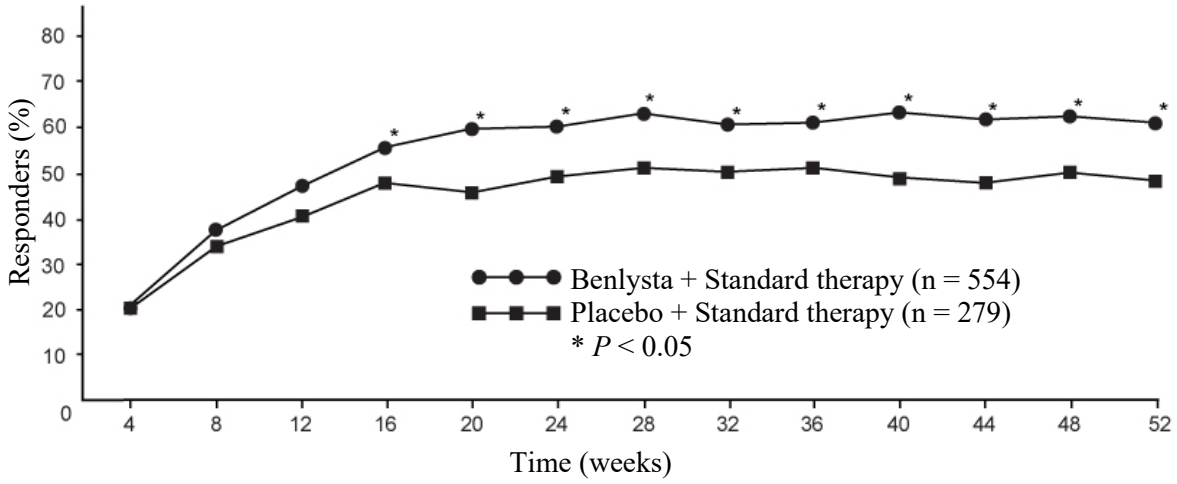
Table 1. Response rate at Week 52

Response[1]	**Placebo**[2] **(n = 279)**	**Benlysta**[2] **200 mg weekly** **(n = 554)**
SLE responder index Observed difference vs. placebo Odds ratio (95 % CI) vs. placebo	48.4 %	61.4 % (p = 0.0006) 12.98 % 1.68 (1.25, 2.25)
Components of SLE responder index		
Percent of patients with reduction in SELENA-SLEDAI ≥ 4	49.1 %	62.3 % (p = 0.0005)
Percent of patients with no worsening by BILAG index	74.2 %	80.9 % (p = 0.0305)
Percent of patients with no worsening by PGA	72.8 %	81.2 % (p = 0.0061)

[1] Analyses excluded any subject missing a baseline assessment for any of the components (1 for placebo; 2 for Benlysta).
[2] All patients received standard therapy.

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



Flares in SLE were defined by the modified SELENA SLEDAI SLE Flare Index. The risk of first flare was reduced by 22 % during the 52 weeks of observation in the group receiving Benlysta compared with the group receiving placebo (hazard ratio = 0.78; p = 0.0061). The median time to the first flare among patients having a flare was delayed in patients receiving Benlysta compared with placebo (190 days vs. 141 days). Severe flares were observed in 10.6 % of patients in the group receiving Benlysta compared with 18.2 % of patients in the group receiving placebo over the 52 weeks of observation (observed treatment difference = -7.6 %). The risk of severe flares was reduced by 49 % during the 52 weeks of observation in the group receiving Benlysta compared with the group receiving placebo (hazard ratio = 0.51; p = 0.0004). The median time to the first severe flare among patients having a severe flare was delayed in patients receiving Benlysta compared with placebo (171 days vs. 118 days).

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 ≤ 7.5 mg/day during Weeks 40 through 52, was 18.2 % in the group receiving Benlysta and 11.9 % in the group receiving placebo (p = 0.0732).

Benlysta demonstrated improvement in fatigue compared with placebo measured by the FACIT-Fatigue Scale. The adjusted mean change of score at Week 52 from baseline is significantly greater with Benlysta compared to placebo (4.4 vs. 2.7, p = 0.0130).

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 ≥ 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 2 for results of this example of a higher disease activity group.

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

Subgroup	**Anti-dsDNA positive AND low complement**	
	Placebo	**Benlysta 200 mg weekly**
	(n = 108)	(n = 246)
SRI response rate at Week 52[1] (%)	47.2	64.6 (p = 0.0014)
Observed treatment difference vs. placebo (%)		17.41
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 24 through 52[2] (%)	11.4	20.7 (p = 0.0844)
Observed treatment difference vs. placebo (%)		9.3
	(n = 108)	(n = 248)
FACIT-fatigue score improvement from baseline at Week 52 (mean):	2.4	4.6 (p = 0.0324)
Observed treatment difference vs. placebo (median difference)		2.1

[1] Analysis of SRI response rate at Week 52 excluded any subject missing a baseline assessment (2 for Benlysta).

[2] Among patients with baseline prednisone dose > 7.5 mg/day.

The efficacy and safety of Benlysta in combination with a single cycle of rituximab have been studied in a Phase III, randomised, double-blind, placebo-controlled 104-week study including 292 patients (BLISS-BELIEVE). The primary endpoint was the proportion of subjects with a state of disease control defined as a

SLEDAI-2K score ≤ 2, achieved without immunosuppressants and with corticosteroids at a prednisone equivalent dose of ≤ 5 mg/day at Week 52. This was achieved in 19.4 % (n = 28/144) of the patients treated with Benlysta in combination with rituximab and in 16.7 % (n = 12/72) of the patients treated with Benlysta in combination with placebo (odds ratio 1.27; 95 % CI: 0.60, 2.71; p = 0.5342). A higher frequency of adverse events (91.7 % vs. 87.5 %), serious adverse events (22.2 % vs. 13.9 %) and serious infections (9.0 % vs. 2.8 %) were observed in patients treated with Benlysta in combination with rituximab as compared to Benlysta in combination with placebo.

Lupus nephritis

Subcutaneous injection
The efficacy and safety of Benlysta 200 mg administered subcutaneously to patients with active lupus nephritis is based on data from administration of Benlysta 10 mg/kg body weight intravenously and pharmacokinetic modelling and simulation (see section 5.2).

In the subcutaneous SLE study, described above, patients who had severe active lupus nephritis were excluded; however, 12 % of patients had renal organ domain involvement at baseline (based on SELENA SLEDAI assessment). The following study in active lupus nephritis has been conducted.

Intravenous infusion
The efficacy and safety of Benlysta 10 mg/kg body weight 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. Standard therapy included corticosteroids, 0 to 3 intravenous administrations of methylprednisolone (500 to1000 mg per administration), followed by oral prednisone 0.5 to 1 mg/kg/day with a total daily dose ≤60 mg/day and tapered to ≤ 10 mg/day by Week 24, with:

- mycophenolate mofetil 1 to 3 g/day orally or mycophenolate sodium 720 to 2160 mg/day orally for induction and maintenance, or
- cyclophosphamide 500 mg intravenously every 2 weeks for 6 infusions for induction followed by azathioprine orally at a target dose of 2 mg/kg/day 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 %) 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) ≤ 700 mg/g (79.5 mg/mmol) and estimated glomerular filtration rate (eGFR) ≥ 60 mL/min/1.73 m^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 < 500 mg/g (56.8 mg/mmol) and eGFR ≥ 90 mL/min/1.73 m^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 Benlysta 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 ≤ 700 mg/g (79.5 mg/mmol)	33.6 %	44.4 %	10.8 %	OR 1.54 (1.04, 2.29)	0.0320
eGFR≥ 60 mL/min/1.73 m^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 < 500 mg/g (56.8 mg/mmol)	28.7 %	39.5 %	10.8 %	OR 1.58 (1.05, 2.38)	0.0268
eGFR≥ 90 mL/min/1.73 m^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)]			-	HR 0.51 (0.34, 0.77)	0.0014

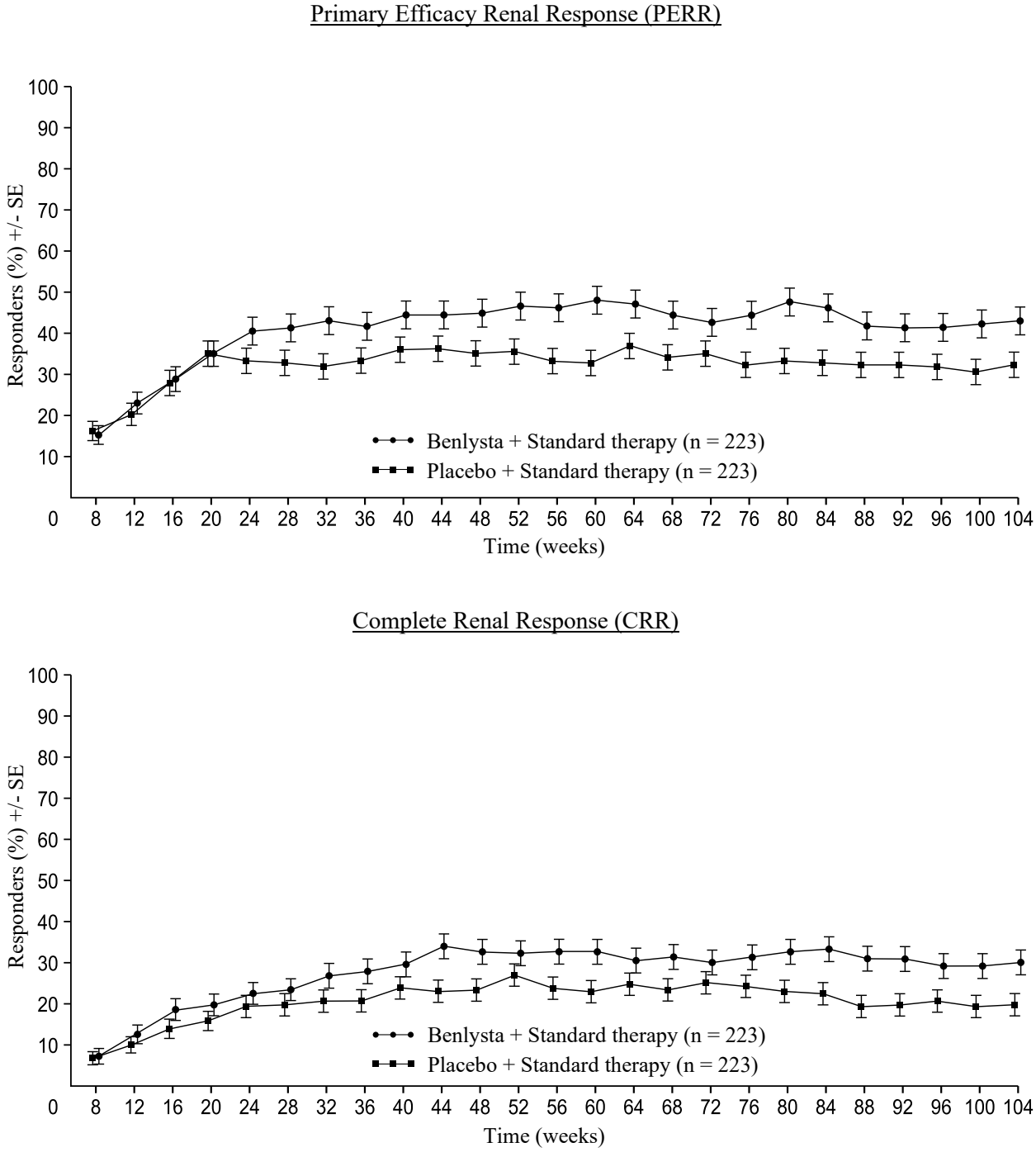
[1] PERR at Week 104 was the primary efficacy analysis; CRR at Week 104, PERR at Week 52 and time to renal-related event or death were included in the pre-specified testing hierarchy.

[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.

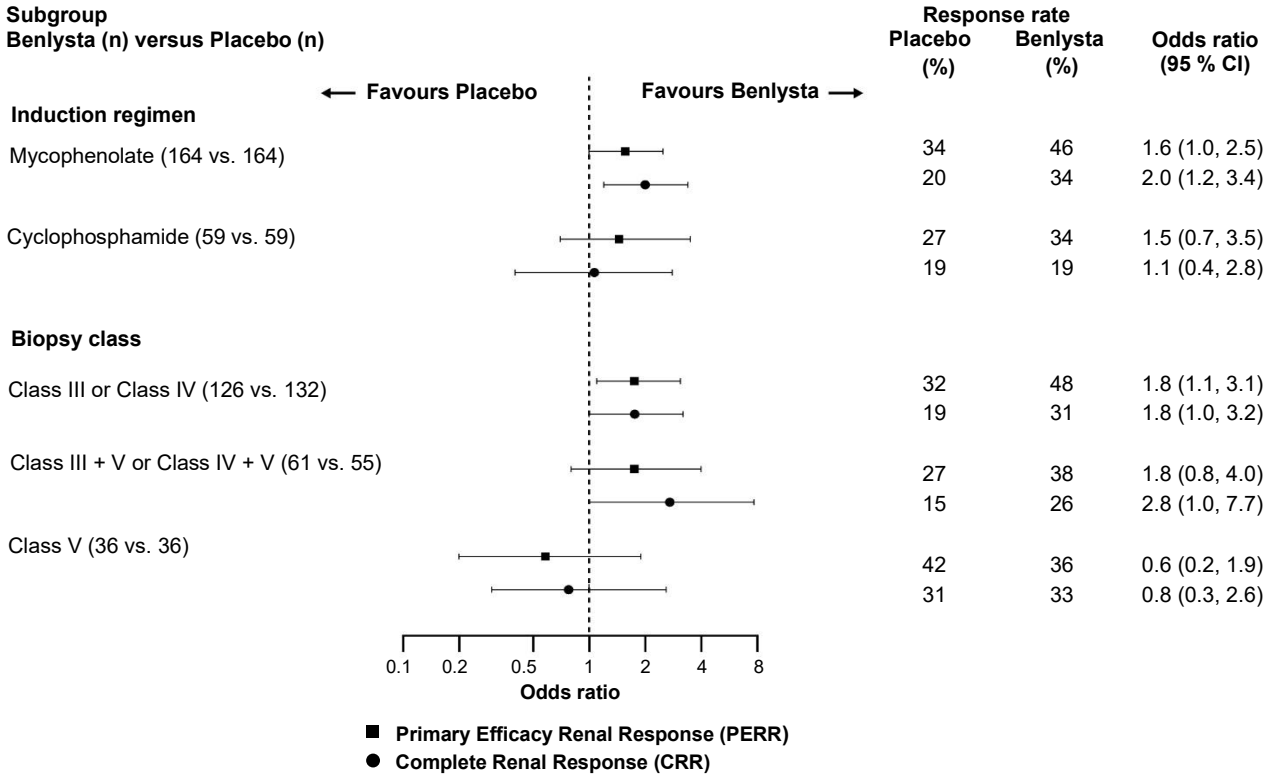
A numerically greater percentage of patients receiving Benlysta achieved PERR beginning at Week 24 compared with placebo, and this treatment difference was maintained through to Week 104. Beginning at Week 12, a numerically greater percentage of patients receiving Benlysta achieved CRR compared with placebo and the numerical difference was maintained through to Week 104 (Figure 2).

Figure 2. Response rates in adults with lupus nephritis by visit



In descriptive subgroup analyses, key efficacy endpoints (PERR and CRR) were examined by induction regimen (mycophenolate or cyclophosphamide) and biopsy class (Class III or IV, Class III + V or Class IV + V, or Class V) (Figure 3).

Figure 3. Odds ratio of PERR and CRR at Week 104 across subgroups



<u>*Age and race*</u>

Age
There were no observed differences in efficacy or safety in SLE patients ≥ 65 years who received Benlysta intravenously or subcutaneously compared to the overall population in placebo-controlled studies; however, the number of patients aged ≥ 65 years (62 patients for efficacy and 219 for safety) is not sufficient to determine whether they respond differently to younger patients.

Black patients
There were too few black patients enrolled in the placebo-controlled studies with subcutaneous Benlysta to draw meaningful conclusions about the effects of race on clinical outcomes.

The safety and efficacy of Benlysta administered intravenously have been studied in black patients. The currently available data are described in the Summary of Product Characteristics of Benlysta 120 mg and 400 mg powder for concentrate for solution for infusion.

<u>Paediatric population</u>

<u>*SLE*</u>

Subcutaneous injection
The safety and efficacy of Benlysta administered subcutaneously to paediatric patients 5 to < 18 years of age with active SLE is supported by a population pharmacokinetic model and simulation integrating data from an open-label pharmacokinetic study of 25 paediatric patients with active SLE administered Benlysta subcutaneously (200908), and a study of paediatric patients with active SLE administered Benlysta intravenously (PLUTO) described below (see section 5.2).

Intravenous infusion
The safety and efficacy of Benlysta was evaluated in a randomised, double-blind, placebo-controlled, 52-week study (PLUTO) in 93 paediatric patients with a clinical diagnosis of SLE according to the ACR classification criteria. Patients had active SLE disease, defined as a SELENA-SLEDAI score ≥ 6 and positive autoantibodies at screening as described in the adult trials. Patients were on a stable SLE treatment regimen (standard of care) and had similar inclusion criteria as the adult studies. Patients who had severe active lupus nephritis, severe active CNS lupus, primary immunodeficiency, IgA deficiency or acute or chronic infections requiring management were excluded from the study. The study was conducted in the US, South America, Europe, and Asia. Patient median age was 15 years (range 6 to 17 years). In the 5- to 11-year-old-group (n = 13) the SELENA-SLEDAI score ranged from 4 to 13, and in 12- to 17-year-old-group (n = 79) the SELENA-SLEDAI score ranged from 4 to 20. The majority (94.6 %) of patients were female. The study was not powered for any statistical comparisons and all data are descriptive.

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 4).

Table 4. Paediatric response rate at Week 52

Response[1]	**Placebo (n = 40)**	**Benlysta 10 mg/kg (n = 53)**
SLE Responder Index (%)	43.6 (17/39)	52.8 (28/53)
Odds ratio (95 % CI) vs. placebo		1.49 (0.64, 3.46)
Components of SLE Responder Index		
Percent of patients with reduction in SELENA-SLEDAI ≥ 4 (%)	43.6 (17/39)	54.7 (29/53)
Odds ratio (95 % CI) vs. placebo		1.62 (0.69, 3.78)
Percent of patients with no worsening by BILAG index (%)	61.5 (24/39)	73.6 (39/53)
Odds ratio (95 % CI) vs. placebo		1.96 (0.77, 4.97)
Percent of patients with no worsening by PGA (%)	66.7 (26/39)	75.5 (40/53)
Odds ratio (95 % CI) vs. placebo		1.70 (0.66, 4.39)

[1] Analyses excluded any subject missing a baseline assessment for any of the components (1 for placebo).

Among patients experiencing a severe flare, the median study day of the first severe flare was Day 150 in the Benlysta group and Day 113 in the placebo group. Severe flares were observed in 17.0 % of the Benlysta group compared to 35.0 % of the placebo group over the 52 weeks of observation (observed treatment difference = 18.0 %; hazard ratio = 0.36, 95 % CI: 0.15, 0.86). 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 receiving Benlysta demonstrated improvement compared with placebo (Table 5).

Table 5. PRINTO/ACR response rate at Week 52

	Proportion of patients with at least 50 % improvement in any 2 of 5 components[1] and no more than one of the remaining worsening by more than 30 %		Proportion of patients with at least 30 % improvement in 3 of 5 components[1] 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)

[1] 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.

5.2 Pharmacokinetic properties

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 Benlysta subcutaneously.

Absorption

Benlysta in the pre-filled pen is administered by subcutaneous injection.

Following subcutaneous administration, the bioavailability of belimumab was approximately 74 %. Steady-state exposure was reached after approximately 11 weeks of subcutaneous administration. The maximum serum concentration (C_{max}) of belimumab at steady state was 108 µg/mL.

Distribution

Belimumab was distributed to tissues with steady-state volume (Vss) of distribution of approximately 5 litres.

Biotransformation

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

Following subcutaneous administration, belimumab had a terminal half-life of 18.3 days. The systemic clearance was 204 mL/day.

Lupus nephritis study

A population pharmacokinetic analysis was conducted in 224 adult patients with lupus nephritis who received Benlysta 10 mg/kg body weight 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 belimumab 10 mg/kg body weight intravenously.

Based on population pharmacokinetic modelling and simulation, the steady-state average concentrations of subcutaneous administration of belimumab 200 mg once weekly in adults with lupus nephritis are predicted to be similar to those observed in adults with lupus nephritis receiving belimumab 10 mg/kg body weight intravenously every 4 weeks.

Special patient populations

Paediatric population: The pharmacokinetic parameters of belimumab administered subcutaneously are based on a population pharmacokinetic analysis of 25 patients from a Phase II pharmacokinetic study in paediatric patients with SLE receiving belimumab subcutaneously and the Phase II study in paediatric patients with SLE receiving belimumab intravenously. Following subcutaneous administration of 200 mg of belimumab in paediatric patients 5 to less than 18 years of age [weekly (patients weighing ≥ 50 kg), every 10 days (patients weighing 30 to < 50 kg) or every 2 weeks (patients weighing 15 to < 30 kg)], the steady state average belimumab concentration is estimated to be similar to that of adult SLE subjects following subcutaneous administration of 200 mg belimumab weekly, and similar to that of paediatric SLE subjects following intravenous administration of belimumab 10 mg/kg body weight on Days 0, 14 and 28, and at 4-week intervals thereafter. Simulated steady-state geometric mean C_{max}, C_{avg}, C_{min}, and AUC (calculated over the dosing interval) are estimated to be 124 µg/mL, 119 µg/mL, 111 µg/mL and 834 day•µg/mL for paediatric patients weighing ≥ 50 kg receiving belimumab once weekly, 114 µg/mL, 105 µg/mL, 91 µg/mL and 1051 day•µg/mL for paediatric patients weighing 30 to < 50 kg receiving belimumab every 10 days, and 119 µg/mL, 103 µg/mL, 79 µg/mL and 1438 day•µg/mL for paediatric patients weighing 15 to < 30 kg receiving belimumab every 2 weeks.

Elderly: Benlysta has been studied in a limited number of elderly patients. Age did not affect belimumab exposure in the subcutaneous population pharmacokinetic analysis. However, given the small number of subjects ≥ 65, an effect of age cannot be ruled out conclusively.

Renal impairment: No specific studies have been conducted to examine the effects of renal impairment on the pharmacokinetics of belimumab. During clinical development, Benlysta was studied in a limited number of SLE patients with mild (creatinine clearance [CrCl] ≥ 60 and < 90 mL/min), moderate (CrCl ≥ 30 and < 60 mL/min), or severe (CrCl ≥ 15 and < 30 mL/min) renal impairment: 121 patients with mild renal impairment and 30 patients with moderate renal impairment received Benlysta subcutaneously; 770 patients with mild renal impairment, 261 patients with moderate renal impairment and 14 patients with severe renal impairment received Benlysta intravenously.

No clinically significant reduction in systemic clearance as a result of renal impairment was observed. Therefore, no dose adjustment is recommended for patients with renal impairment.

Hepatic impairment: No specific studies have been 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 and changes in hepatic function are unlikely to have any effect on the elimination of belimumab.

Body weight/Body mass index (BMI)

The effects of body weight and BMI on belimumab exposure after subcutaneous administration in adults were not considered clinically meaningful. There was no significant impact on efficacy and safety based on weight. Therefore, no dose adjustment in adults is recommended.

The effects of body weight on belimumab exposure after subcutaneous administration in paediatric patients have been determined using a population pharmacokinetic model. Paediatric patients with lower body weight have lower belimumab clearance and volume of distribution resulting in increased exposure. To ensure

belimumab exposures remain within acceptable limits and are consistent across the paediatric weight range, patients with lower body weight are dosed belimumab less frequently (see section 4.2).

Transitioning from intravenous to subcutaneous administration

SLE
Patients with SLE transitioning from 10 mg/kg body weight intravenously every 4 weeks to a 200 mg subcutaneous regimen 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). Based on simulations with population pharmacokinetic parameters, the steady-state average belimumab concentrations for 200 mg subcutaneous every week (in adult patients, and in paediatric patients 5 to under 18 years of age and ≥ 50 kg), every 10 days (in paediatric patients 5 to under 18 years of age and 30 to < 50 kg) or every 2 weeks (in paediatric patients 5 to under 18 years of age and 15 to < 30 kg), were similar to 10 mg/kg body weight intravenous every 4 weeks.

Lupus nephritis
One to 2 weeks after completing the first 2 intravenous doses, patients with lupus nephritis transitioning from 10 mg/kg body weight intravenously to 200 mg subcutaneously weekly, are predicted to have average belimumab serum concentrations similar to patients dosed with 10 mg/kg body weight intravenously every 4 weeks based on population pharmacokinetic simulations (see section 4.2).

5.3 Preclinical safety data

Non-clinical data reveal 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 the 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 body weight by intravenous infusion (approximately 9 times the anticipated maximum human clinical exposure) every 2 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 3 months of life in infant monkeys; IgM levels in infants exposed to belimumab *in utero* recovered by 6 months of age.

Effects on male and female fertility in monkeys were assessed in the 6-month repeat dose toxicology studies of belimumab at doses up to and including 50 mg/kg body weight. No treatment-related changes were noted in the male and female reproductive organs of sexually mature animals. An informal assessment of menstrual cycling in females demonstrated no belimumab-related changes.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Arginine hydrochloride
Histidine
Histidine monohydrochloride
Polysorbate 80 (E 433)
Sodium chloride

Water for injection

6.2 Incompatibilities

None known.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in a refrigerator (2 °C to 8 °C).
Do not freeze.
Store in the original carton in order to protect from light.

A single Benlysta pre-filled pen can be stored at temperatures up to a maximum of 25 °C for a period of up to 12 hours. The pre-filled pen must be protected from light, and discarded if not used within the 12 hour period.

6.5 Nature and contents of container

1 mL solution in a type 1 glass syringe with a fixed needle (stainless steel) in a pre-filled pen.

Available in packs of 1 or 4 pre-filled pens and multipack containing 12 single-dose pre-filled pens (3 packs of 4 pre-filled pens).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Comprehensive instructions for subcutaneous administration of Benlysta in a pre-filled pen are provided at the end of the package leaflet (see Step-by-step instructions).

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

7. MARKETING AUTHORISATION HOLDER

GlaxoSmithKline (Ireland) Limited
12 Riverwalk
Citywest Business Campus
Dublin 24
Ireland

8. MARKETING AUTHORISATION NUMBERS

EU/1/11/700/003 1 pre-filled pen
EU/1/11/700/004 4 pre-filled pens
EU/1/11/700/005 12 (3x4) pre-filled pens (multipack)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 13 July 2011

Date of latest renewal: 18 February 2016

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Benlysta 200 mg solution for injection in pre-filled syringe.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 mL pre-filled syringe contains 200 mg of belimumab.

Belimumab is a human, IgG1λ monoclonal antibody, produced in a mammalian cell line (NS0) by recombinant DNA technology.

Excipient with known effect

Each pre-filled syringe contains 0.1 mg polysorbate 80.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in pre-filled syringe (injection)

A clear to opalescent, colourless to pale yellow solution, with a pH of 6 and an osmolality of 270 – 320 mOsm/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Benlysta is indicated as add-on therapy in adult patients with active, autoantibody-positive systemic lupus erythematosus (SLE) with a high degree of disease activity (e.g., positive anti-dsDNA and low complement) despite standard therapy (see section 5.1).

Benlysta is indicated in combination with background immunosuppressive therapies for the treatment of adult patients with active lupus nephritis (see sections 4.2 and 5.1).

4.2 Posology and method of administration

Benlysta treatment should be initiated and supervised by a qualified physician experienced in the diagnosis and treatment of SLE. It is recommended that the first subcutaneous injection of Benlysta is given under the supervision of a healthcare professional in a setting that is sufficiently qualified to manage hypersensitivity reactions, if necessary. The healthcare professional must provide proper training in subcutaneous technique and education about signs and symptoms of hypersensitivity reactions (see section 4.4). A patient may self-inject, or the patient caregiver may administer Benlysta after the healthcare professional determines that it is appropriate.

Posology

SLE

The recommended dose is 200 mg once weekly, administered subcutaneously. Dosing is not based on weight (see section 5.2). The patient's condition should be evaluated continuously. Discontinuation of treatment with Benlysta is to be considered if there is no improvement in disease control after 6 months of treatment.

Lupus nephritis

In patients initiating therapy with Benlysta for active lupus nephritis, the recommended dosage regimen is a 400 mg dose (two 200 mg injections) once weekly for 4 doses, then 200 mg once weekly thereafter. In patients continuing therapy with Benlysta for active lupus nephritis, the recommended dosage is 200 mg once weekly. Benlysta is to be used in combination with corticosteroids and mycophenolate or cyclophosphamide for induction, or mycophenolate or azathioprine for maintenance. The patient's condition should be evaluated continuously.

Missed doses

If a dose is missed, it is recommended to be administered as soon as possible. Thereafter, patients can resume dosing on their usual day of administration, or start a new schedule from the day that the missed dose was administered.

Changing the scheduled dosing day

If patients wish to change their scheduled dosing day, a new dose can be given on the newly preferred day of the week. Thereafter the patient can continue with the new schedule from that day, even if the dosing interval may be temporarily less than usual.

Transition from intravenous to subcutaneous administration

SLE
If a patient with SLE is being transitioned from Benlysta intravenous administration to subcutaneous administration, the first subcutaneous injection must be administered 1 to 4 weeks after the last intravenous dose (see section 5.2).

Lupus nephritis
If a patient with lupus nephritis is being transitioned from Benlysta intravenous administration to subcutaneous administration, it is recommended that the first dose of 200 mg subcutaneous injection be administered 1 to 2 weeks after the last intravenous dose. This transition can occur any time after the patient completes the first 2 intravenous doses (see section 5.2).

Special populations

Elderly

Data on patients ≥ 65 years are limited (see section 5.1). Benlysta should be used with caution in the elderly. Dose adjustment is not required (see section 5.2).

Renal impairment

Belimumab has been studied in a limited number of SLE patients with renal impairment. On the basis of the available information, dose 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 lack of data (see section 5.2).

Hepatic impairment

No specific studies with Benlysta have been conducted in patients with hepatic impairment. Patients with hepatic impairment are unlikely to require dose adjustment (see section 5.2).

Paediatric population

SLE
In patients 5 years to less than 18 years of age, subcutaneous administration of Benlysta with the pre-filled syringe has not been evaluated and subcutaneous administration of Benlysta with the pre-filled pen is recommended. Currently available data are described in sections 4.8, 5.1 and 5.2, but no recommendation on a posology can be made with Benlysta in a pre-filled syringe.

The safety and efficacy of Benlysta subcutaneous administration in children under 5 years of age or less than 15 kg have not been established. No data are available.

Lupus nephritis
The safety and efficacy of Benlysta subcutaneous administration in children and adolescents under 18 years of age have not been established. No data are available.

Method of administration

The pre-filled syringe must be used for subcutaneous injection only. The recommended injection sites are the abdomen or thigh. When injecting in the same region, patients must be advised to use a different injection site for each injection; injections must not be given into areas where the skin is tender, bruised, red, or hard. When a 400 mg dose is administered at the same site, it is recommended that the 2 individual 200 mg injections are administered at least 5 cm (approximately 2 inches) apart.

Comprehensive instructions for subcutaneous administration of Benlysta in a pre-filled syringe are provided at the end of the package leaflet (see Step-by-step instructions).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

In order to improve traceability of biological medicinal products, the tradename and the batch number of the administered product should be clearly recorded.

Benlysta has not been studied in the following patient groups and is not recommended in:

- severe active central nervous system lupus
- 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

Available data do not support the co-administration of rituximab with Benlysta in patients with SLE (see section 5.1). Caution needs to be exercised if Benlysta is co-administered with other B cell targeted therapy.

Hypersensitivity

Administration of subcutaneous or intravenous Benlysta may result in hypersensitivity reactions which can be severe, and fatal. In the event of a severe reaction, Benlysta administration must be interrupted and appropriate medical therapy administered (see section 4.2). The risk of hypersensitivity reactions is greatest with the first two doses; however, the risk must be considered for every administration. Patients with a history of multiple drug allergies or significant hypersensitivity may be at increased risk. Recurrence of clinically significant reactions after initial appropriate treatment of symptoms has also been observed (see sections 4.2 and 4.8).

Patients must be advised that hypersensitivity reactions are possible, on the day of, or several days after administration, and be informed of potential signs and symptoms and the possibility of recurrence. Patients must be instructed to seek immediate medical attention if they experience any of these symptoms. The package leaflet must be available to the patient. Delayed-type, non-acute hypersensitivity reactions have also been observed and included symptoms such as rash, nausea, fatigue, myalgia, headache, and facial oedema.

In intravenous clinical studies, serious infusion and hypersensitivity reactions included anaphylactic reaction, bradycardia, hypotension, angioedema, and dyspnoea. Please refer to the Summary of Product Characteristics for Benlysta powder for concentrate for solution for infusion (section 4.4).

Infections

The mechanism of action of belimumab could increase the risk for the development of infections in adults and children with lupus, including opportunistic infections, and younger children may be at increased risk. In controlled clinical studies, the incidence of serious infections was similar across the Benlysta and placebo groups; however, fatal infections (e.g. pneumonia and sepsis) occurred more frequently in patients receiving Benlysta compared with placebo (see section 4.8). Pneumococcal vaccination should be considered before initiating Benlysta treatment. Benlysta must not be initiated in patients with active serious infections (including serious chronic infections). Physicians need to exercise caution and carefully assess if the benefits are expected to outweigh the risks when considering the use of Benlysta in patients with a history of recurrent infection. Physicians need to advise patients to contact their health care provider if they develop symptoms of an infection. Patients who develop an infection while undergoing treatment with Benlysta must be monitored closely and careful consideration given to interrupting immunosuppressant therapy including Benlysta until the infection is resolved. The risk of using Benlysta in patients with active or latent tuberculosis is unknown.

Depression and suicidality

In controlled clinical intravenous and subcutaneous studies, psychiatric disorders (depression, suicidal ideation and behaviour including suicides) have been reported more frequently in patients receiving Benlysta (see section 4.8). Physicians should 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 must advise patients (and caregivers where appropriate) to contact their health care provider about new or worsening psychiatric symptoms. In patients who experience such symptoms, treatment discontinuation is to be considered.

Severe cutaneous adverse reactions

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), which can be life-threatening or fatal, have been reported in association with Benlysta treatment. Patients should be advised of the signs and symptoms of SJS and TEN and monitored closely for skin reactions. If signs and symptoms suggestive of

these reactions appear, Benlysta should be withdrawn immediately, and an alternative treatment should be considered. If the patient has developed SJS or TEN with the use of Benlysta, treatment with Benlysta must not be restarted in this patient at any time.

Progressive multifocal leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) has been reported with Benlysta treatment for SLE. Physicians must be particularly alert to symptoms suggestive of PML that patients may not notice (e.g., cognitive, neurological or psychiatric symptoms or signs). Patients should be monitored for any of these new or worsening symptoms or signs, and if such symptoms/signs occur, referral to a neurologist and appropriate diagnostic measures for PML must be considered as clinically indicated. If PML is suspected, immunosuppressant therapy, including Benlysta, must be suspended until PML has been excluded. If PML is confirmed, immunosuppressant therapy, including Benlysta, must be discontinued.

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, belimumab may interfere with the response to immunisations. However, in a small 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 receiving standard immunosuppressive treatment at the time of vaccination. There are insufficient data to draw conclusions regarding response to other vaccines.

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. In a substudy, a small group of patients who had previously received either tetanus, pneumococcal or influenza vaccinations were found to maintain protective titres after treatment with Benlysta.

Malignancies and lymphoproliferative disorders

Immunomodulatory medicinal products, including Benlysta, may increase the risk of malignancy. Caution is advised when considering Benlysta therapy for patients with a history of malignancy or when considering continuing treatment in patients who develop malignancy. Patients with malignant neoplasm within the last 5 years have not been studied, with the exception of those with basal or squamous cell cancers of the skin, or cancer of the uterine cervix, that has been fully excised or adequately treated.

Polysorbate 80 content

This medicinal product contains polysorbate 80 (see section 2), which may cause allergic reactions.

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

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 is to be considered for patients being treated with CYP substrates with a narrow therapeutic index, where the dose is individually adjusted (e.g. warfarin).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

Women of childbearing potential must use effective contraception during Benlysta treatment and for at least 4 months after the last treatment.

Pregnancy

There are a limited amount of data from the use of Benlysta in pregnant women. Besides an expected pharmacological effect i.e. reduction of B cells, animal studies in monkeys do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). Benlysta should not be used during pregnancy unless the potential benefit justifies the potential risk to the foetus.

Breast-feeding

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 monkeys administered 150 mg/kg body weight every 2 weeks.

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

Fertility

There are no data on the effects of belimumab on human fertility. Effects on male and female fertility have not been formally evaluated in animal studies (see section 5.3).

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. No detrimental effects on such activities are predicted from the pharmacology of belimumab. It is recommended that the clinical status of the subject and the adverse reaction profile of Benlysta be borne in mind when considering the patient's ability to perform tasks that require judgement, motor or cognitive skills.

4.8 Undesirable effects

Summary of the safety profile

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

The data presented in the table below reflect exposure in 674 patients with SLE from the three pre-registration clinical studies and 470 patients in the subsequent placebo-controlled study administered Benlysta intravenously (10 mg/kg body weight over a 1-hour period on Days 0, 14, 28, and then every 28 days for up to 52 weeks), and 556 patients with SLE exposed to 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 body weight 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 medicinal products, anti-malarials, non-steroidal anti-inflammatory medicinal products.

Adverse reactions were reported in 84 % of Benlysta-treated patients and 87 % of placebo-treated patients. The most frequently reported adverse reaction (≥ 5 % of patients with SLE treated with Benlysta plus standard of care and at a rate ≥ 1 % greater than placebo) was nasopharyngitis. The proportion of patients who discontinued treatment due to adverse reactions was 7 % for Benlysta-treated patients and 8 % for placebo-treated patients.

The most frequently reported adverse reactions (> 5 % of patients with active lupus nephritis treated with Benlysta plus standard of care) were upper respiratory tract infection, urinary tract infection, and herpes zoster. The proportion of patients who discontinued treatment due to adverse reactions was 12.9 % for Benlysta-treated patients and 12.9 % for placebo-treated patients.

Severe cutaneous adverse reactions: Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported in association with Benlysta treatment (see section 4.4).

Tabulated list of adverse reactions

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

Very common	≥ 1/10
Common	≥ 1/100 to < 1/10
Uncommon	≥ 1/1000 to < 1/100
Rare	≥ 1/10 000 to < 1/1000
Not known	cannot be estimated from the available data.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. The frequency given is the highest seen with either formulation.

System organ class	Frequency	Adverse reactions
Infections and infestations[1]	Very common	Bacterial infections, e.g. bronchitis, urinary tract infection
	Common	Gastroenteritis viral, pharyngitis, nasopharyngitis, viral upper respiratory tract infection
Blood and lymphatic system disorders	Common	Leucopenia
Immune system disorders	Common	Hypersensitivity reactions[2]
	Uncommon	Anaphylactic reaction
	Rare	Delayed-type, non-acute hypersensitivity reactions
Psychiatric disorders	Common	Depression
	Uncommon	Suicidal behaviour, suicidal ideation
Nervous system disorders	Common	Migraine
Gastrointestinal disorders	Common	Diarrhoea, nausea
Skin and subcutaneous tissue disorders	Common	Injection site reactions[3], urticaria, rash
	Uncommon	Angioedema
	Not known	Stevens-Johnson syndrome, toxic epidermal necrolysis
Musculoskeletal and connective tissue disorders	Common	Pain in extremity
General disorders and administration site conditions	Common	Infusion or injection-related systemic reactions[2], pyrexia

[1] See 'Description of selected adverse reactions' and section 4.4 'Infections' for further information.
[2] '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.
[3] Applies to subcutaneous formulation only.

Description of selected adverse reactions

Data presented below are pooled from the three pre-registration intravenous clinical studies (10 mg/kg body weight intravenous dose only) and the subcutaneous clinical study. 'Infections' and 'Psychiatric disorders' also include data from a post-marketing study.

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.

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 receiving Benlysta and in no patients receiving placebo.

Infections: The overall incidence of infections in intravenous and subcutaneous pre-registration SLE studies was 63 % in both groups receiving Benlysta or placebo. Infections occurring in at least 3 % of patients receiving Benlysta and at least 1 % more frequently than patients receiving placebo were viral upper respiratory tract infection, bronchitis, and urinary tract infection bacterial. Serious infections occurred in 5 % of patients in both groups receiving Benlysta or placebo*;* serious opportunistic infections accounted for 0.4 % and 0 % of these, respectively. Infections leading to discontinuation of treatment occurred in 0.7 % of patients receiving Benlysta and 1.5 % of patients receiving placebo. Some infections were severe or fatal.

For information on infections observed in paediatric patients with SLE see Paediatric population section below.

In the lupus nephritis study, patients were receiving a background of standard therapy (see section 5.1) 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.

In a randomised, double-blind, 52-week, post-marketing safety SLE study (BEL115467) which assessed mortality and specific adverse events in adults, serious infections occurred in 3.7 % of patients receiving Benlysta (10 mg/kg body weight intravenously) vs. 4.1 % of patients receiving placebo. However, fatal infections (e.g. pneumonia and sepsis) occurred in 0.45 % (9/2002) of Benlysta-treated patients vs. 0.15 % (3/2001) of patients receiving placebo, while the incidence of all-cause mortality was 0.50 % (10/2002) vs. 0.40 % (8/2001), respectively. Most fatal infections were observed during the first 20 weeks of treatment with Benlysta.

Psychiatric disorders: In the pre-registration intravenous SLE clinical studies, serious psychiatric events were reported in 1.2 % (8/674) of patients receiving Benlysta 10 mg/kg body weight 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 body weight and 0.3 % (2/675) of patients receiving placebo. There were two suicides in Benlysta-treated patients (including one receiving Benlysta 1 mg/kg body weight).

In a 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) of patients receiving placebo. The overall incidence of serious suicidal ideation or behaviour or self-injury without suicidal intent was 0.7 % (15/2002) in patients receiving Benlysta and 0.2 % (5/2001) in the placebo group. No suicide was reported in either group.

The intravenous SLE studies above 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.

Leucopenia: The incidence of leucopenia reported in patients with SLE as an adverse event was 3 % in the group receiving Benlysta and 2 % in the group receiving placebo.

Injection site reactions: In the subcutaneous SLE 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.

Paediatric population

The adverse reaction profile in paediatric patients is based on one subcutaneous study and one intravenous study.

In a 52-week open-label study in which 25 paediatric patients (10 to 17 years of age) with SLE received subcutaneous Benlysta at a comparable exposure to adults (200 mg at a set dosing interval based on body weight, on a background of concomitant treatments), the safety profile in paediatric patients receiving Benlysta subcutaneously was consistent with the known safety profile for belimumab.

In a 52-week placebo-controlled study in which 53 patients (6 to 17 years of age) with SLE received Benlysta (10 mg/kg body weight intravenously on Days 0, 14, 28, and then every 28 days, on a background of concomitant treatments), no new safety signals were observed in the paediatric population 12 years of age and above (n = 43). Safety data in children younger than 12 years of age (n = 10) are limited.

Infections
5- to 11-year-old group: infections were reported in 8/10 patients receiving Benlysta intravenously and 3/3 patients receiving placebo, and serious infections were reported in 1/10 patients receiving Benlysta intravenously and 2/3 patients receiving placebo (see section 4.4).
12- to 17-year-old group: infections were reported in 22/43 patients receiving Benlysta intravenously and 25/37 patients receiving placebo, and serious infections were reported in 3/43 patients receiving Benlysta intravenously and 3/37 patients receiving placebo. In the open-label extension phase there was one fatal infection in a patient receiving Benlysta intravenously.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via the national reporting system listed in Appendix V.

4.9 Overdose

There is limited clinical experience with overdose 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 body weight 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 body weight.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, monoclonal antibodies, ATC code: L04AG04

Mechanism of action

Belimumab is a human IgG1λ monoclonal antibody specific for soluble human B Lymphocyte Stimulator protein (BLyS, also referred to as BAFF and TNFSF13B). Belimumab blocks the binding of soluble BLyS, a B cell survival factor, to its receptors on B cells. 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.

BLyS levels are elevated in patients with SLE and other autoimmune diseases. There is an association between plasma BLyS levels and SLE disease activity. The relative contribution of BLyS levels to the pathophysiology of SLE is not fully understood.

Pharmacodynamic effects

Median IgG levels at Week 52 were reduced by 11 % in patients with SLE receiving Benlysta 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 Benlysta compared with 41 % in patients receiving placebo. In patients with anti-dsDNA antibodies at baseline, by Week 52, 18 % of patients treated with Benlysta had converted to anti-dsDNA negative compared with 15 % of the patients receiving placebo.

In patients with SLE with low complement levels, normalization of C3 and C4 was observed by Week 52 in 42 % and 53 % of patients receiving Benlysta and in 21 % and 20 % of patients receiving placebo, respectively.

Benlysta significantly reduced circulating overall, transitional, naïve, and SLE B cells, as well as plasma cells 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.

The B cell and IgG response to long term treatment with intravenous Benlysta was assessed in an uncontrolled SLE extension study. After 7 and a half years of treatment (including the 72-week parent study), a substantial and sustained decrease in various B cell subsets was observed leading to 87 % median reduction in naïve B cells, 67 % in memory B cells, 99 % in activated B cells, and 92 % median reduction 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 Benlysta (10 mg/kg body weight intravenously) 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 Benlysta group as expected with the known mechanism of belimumab. At Week 104, the median percent increase from baseline in IgG was 17 % for Benlysta 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 one intravenous study in paediatric patients with SLE (6 to 17 years of age) and one subcutaneous study in paediatric patients with SLE (10 to 17 years of age), the pharmacodynamic response was consistent with the adult data (see section 4.2).

Immunogenicity

In the subcutaneous study where serum samples from more than 550 adult patients with SLE were tested, no anti-belimumab antibodies were detected during or after treatment with belimumab 200 mg subcutaneously. In the lupus nephritis study where 224 adult patients received Benlysta 10 mg/kg body weight intravenously, no anti-belimumab antibodies were detected.

In one intravenous study in 6- to 17-year-old paediatric patients (n = 53) with SLE and one subcutaneous study in 10- to 17-year-old paediatric patients (n = 25) with SLE, none of the patients developed anti-belimumab antibodies (see section 4.2).

Clinical efficacy and safety

SLE

Subcutaneous injection
The efficacy of Benlysta administered subcutaneously was evaluated in a randomised, double-blind, placebo-controlled 52-week Phase III study (HGS1006-C1115; BEL112341) in 836 adult 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 ≥ 8 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.

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. Background medicinal products included corticosteroids (86 %; > 7.5 mg/day prednisone equivalent 60 %), immunosuppressives (46 %), and anti-malarials (69 %). Patients were randomised in a 2:1 ratio to receive belimumab 200 mg or placebo subcutaneously once weekly for 52 weeks.

At baseline 62.2 % of patients had high disease activity (SELENA SLEDAI score ≥ 10), 88 % of patients had mucocutaneous, 78 % had musculoskeletal, 8 % had haematological, 12 % had renal, and 8 % had vascular organ involvement.

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 measures improvement in SLE disease activity, without worsening in any organ system, or in the patient's overall condition.

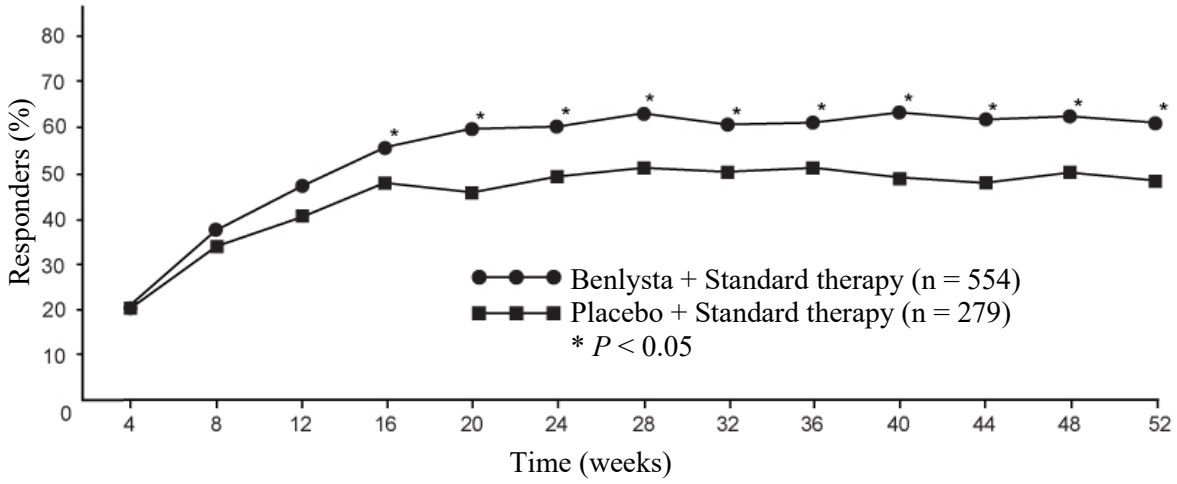
Table 1. Response rate at Week 52

Response[1]	**Placebo**[2] **(n = 279)**	**Benlysta**[2] **200 mg weekly** **(n = 554)**
SLE responder index Observed difference vs. placebo Odds ratio (95 % CI) vs. placebo	48.4 %	61.4 % (p = 0.0006) 12.98 % 1.68 (1.25, 2.25)
Components of SLE responder index		
Percent of patients with reduction in SELENA-SLEDAI ≥ 4	49.1 %	62.3 % (p = 0.0005)
Percent of patients with no worsening by BILAG index	74.2 %	80.9 % (p = 0.0305)
Percent of patients with no worsening by PGA	72.8 %	81.2 % (p = 0.0061)

[1] Analyses excluded any subject missing a baseline assessment for any of the components (1 for placebo; 2 for Benlysta).
[2] All patients received standard therapy.

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



Flares in SLE were defined by the modified SELENA SLEDAI SLE Flare Index. The risk of first flare was reduced by 22 % during the 52 weeks of observation in the group receiving Benlysta compared with the group receiving placebo (hazard ratio = 0.78; p = 0.0061). The median time to the first flare among patients having a flare was delayed in patients receiving Benlysta compared with placebo (190 days vs. 141 days). Severe flares were observed in 10.6 % of patients in the group receiving Benlysta compared with 18.2 % of patients in the group receiving placebo over the 52 weeks of observation (observed treatment difference = -7.6 %). The risk of severe flares was reduced by 49 % during the 52 weeks of observation in the group receiving Benlysta compared with the group receiving placebo (hazard ratio = 0.51; p = 0.0004). The median time to the first severe flare among patients having a severe flare was delayed in patients receiving Benlysta compared with placebo (171 days vs. 118 days).

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 ≤ 7.5 mg/day during Weeks 40 through 52, was 18.2 % in the group receiving Benlysta and 11.9 % in the group receiving placebo (p = 0.0732).

Benlysta demonstrated improvement in fatigue compared with placebo measured by the FACIT-Fatigue Scale. The adjusted mean change of score at Week 52 from baseline is significantly greater with Benlysta compared to placebo (4.4 vs. 2.7, p = 0.0130).

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 ≥ 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 2 for results of this example of a higher disease activity group.

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

Subgroup	**Anti-dsDNA positive AND low complement**	
	Placebo	**Benlysta 200 mg weekly**
	(n = 108)	(n = 246)
SRI response rate at Week 52[1] (%)	47.2	64.6 (p = 0.0014)
Observed treatment difference vs. placebo (%)		17.41
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 24 through 52[2] (%)	11.4	20.7 (p = 0.0844)
Observed treatment difference vs. placebo (%)		9.3
	(n = 108)	(n = 248)
FACIT-fatigue score improvement from baseline at Week 52 (mean):	2.4	4.6 (p = 0.0324)
Observed treatment difference vs. placebo (median difference)		2.1

[1] Analysis of SRI response rate at Week 52 excluded any subject missing a baseline assessment (2 for Benlysta).

[2] Among patients with baseline prednisone dose > 7.5 mg/day.

The efficacy and safety of Benlysta in combination with a single cycle of rituximab have been studied in a Phase III, randomised, double-blind, placebo-controlled 104-week study including 292 patients (BLISS-BELIEVE). The primary endpoint was the proportion of subjects with a state of disease control defined as a

SLEDAI-2K score ≤ 2, achieved without immunosuppressants and with corticosteroids at a prednisone equivalent dose of ≤ 5 mg/day at Week 52. This was achieved in 19.4 % (n = 28/144) of the patients treated with Benlysta in combination with rituximab and in 16.7 % (n = 12/72) of the patients treated with Benlysta in combination with placebo (odds ratio 1.27; 95 % CI: 0.60, 2.71; p = 0.5342). A higher frequency of adverse events (91.7 % vs. 87.5 %), serious adverse events (22.2 % vs. 13.9 %) and serious infections (9.0 % vs. 2.8 %) were observed in patients treated with Benlysta in combination with rituximab as compared to Benlysta in combination with placebo.

Lupus nephritis

Subcutaneous injection
The efficacy and safety of Benlysta 200 mg administered subcutaneously to patients with active lupus nephritis is based on data from administration of Benlysta 10 mg/kg body weight intravenously and pharmacokinetic modelling and simulation (see section 5.2).

In the subcutaneous SLE study, described above, patients who had severe active lupus nephritis were excluded; however, 12 % of patients had renal organ domain involvement at baseline (based on SELENA SLEDAI assessment). The following study in active lupus nephritis has been conducted.

Intravenous infusion
The efficacy and safety of Benlysta 10 mg/kg body weight 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. Standard therapy included corticosteroids, 0 to 3 intravenous administrations of methylprednisolone (500 to1000 mg per administration), followed by oral prednisone 0.5 to1 mg/kg/day with a total daily dose ≤60 mg/day and tapered to ≤ 10 mg/day by Week 24, with:

- mycophenolate mofetil 1 to 3 g/day orally or mycophenolate sodium 720 to 2160 mg/day orally for induction and maintenance, or
- cyclophosphamide 500 mg intravenously every 2 weeks for 6 infusions for induction followed by azathioprine orally at a target dose of 2 mg/kg/day 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 %) 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) ≤ 700 mg/g (79.5 mg/mmol) and estimated glomerular filtration rate (eGFR) ≥ 60 mL/min/1.73 m^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 < 500 mg/g (56.8 mg/mmol) and eGFR ≥ 90 mL/min/1.73 m^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 Benlysta 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 ≤ 700 mg/g (79.5 mg/mmol)	33.6 %	44.4 %	10.8 %	OR 1.54 (1.04, 2.29)	0.0320
eGFR≥ 60 mL/min/1.73 m^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 < 500 mg/g (56.8 mg/mmol)	28.7 %	39.5 %	10.8 %	OR 1.58 (1.05, 2.38)	0.0268
eGFR≥ 90 mL/min/1.73 m^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)]			-	HR 0.51 (0.34, 0.77)	0.0014

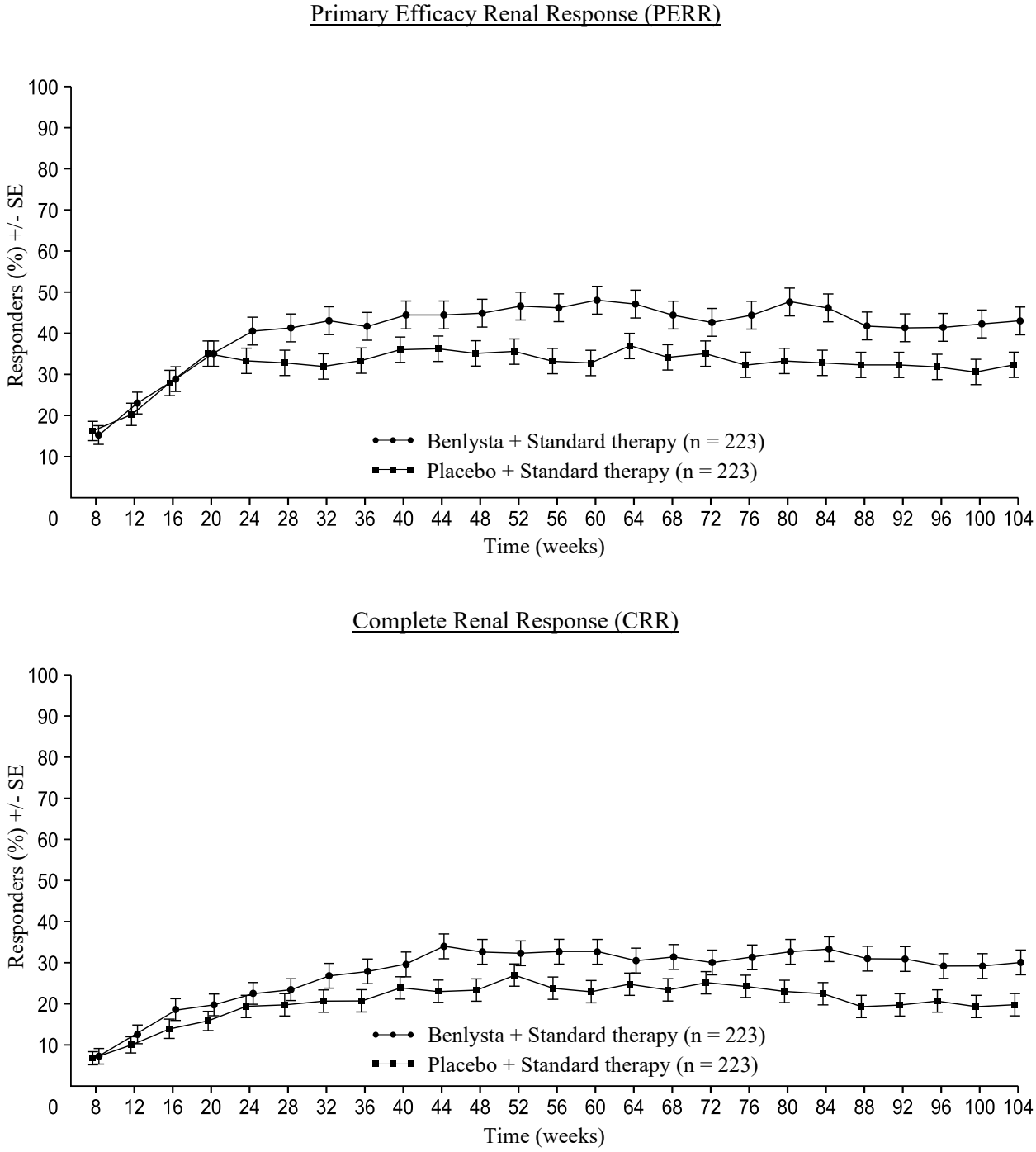
[1] PERR at Week 104 was the primary efficacy analysis; CRR at Week 104, PERR at Week 52 and time to renal-related event or death were included in the pre-specified testing hierarchy.

[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.

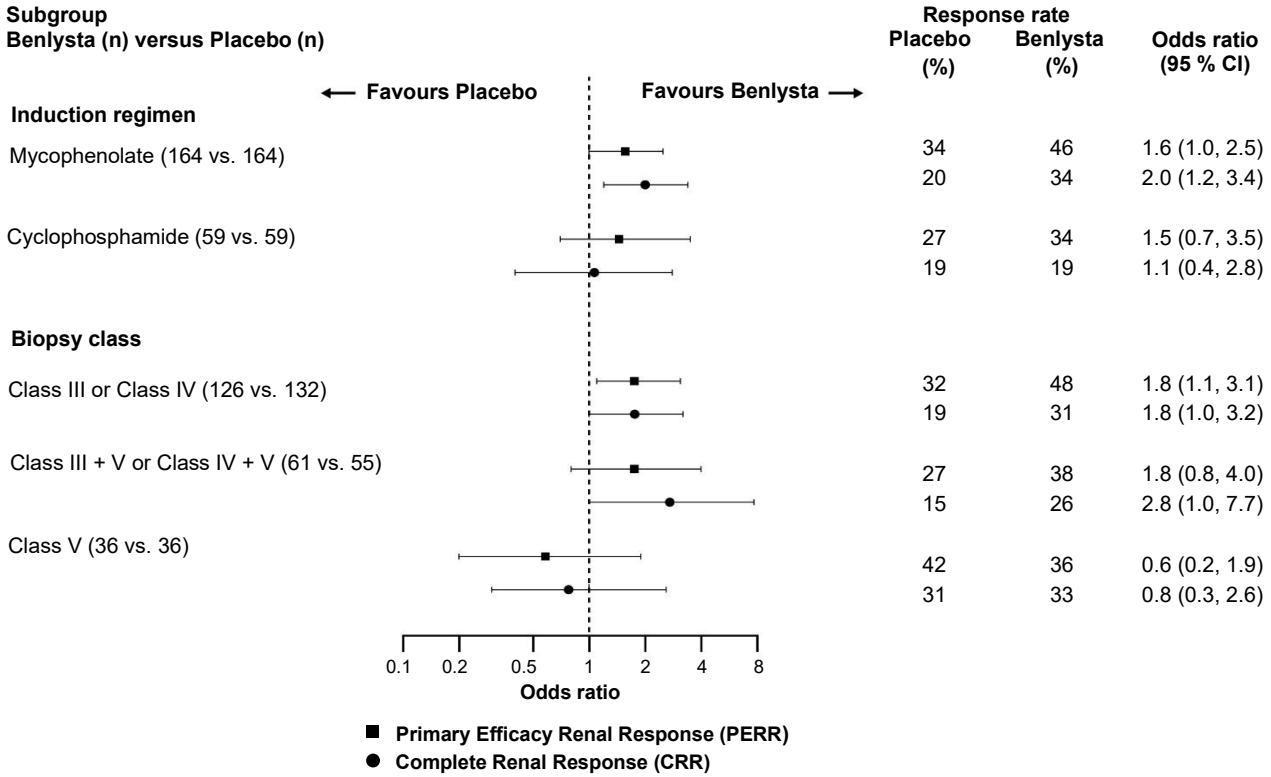
A numerically greater percentage of patients receiving Benlysta achieved PERR beginning at Week 24 compared with placebo, and this treatment difference was maintained through to Week 104. Beginning at Week 12, a numerically greater percentage of patients receiving Benlysta achieved CRR compared with placebo and the numerical difference was maintained through to Week 104 (Figure 2).

Figure 2. Response rates in adults with lupus nephritis by visit



In descriptive subgroup analyses, key efficacy endpoints (PERR and CRR) were examined by induction regimen (mycophenolate or cyclophosphamide) and biopsy class (Class III or IV, Class III + V or Class IV + V, or Class V) (Figure 3).

Figure 3. Odds ratio of PERR and CRR at Week 104 across subgroups



<u>*Age and race*</u>

Age
There were no observed differences in efficacy or safety in SLE patients ≥ 65 years who received Benlysta intravenously or subcutaneously compared to the overall population in placebo-controlled studies; however, the number of patients aged ≥ 65 years (62 patients for efficacy and 219 for safety) is not sufficient to determine whether they respond differently to younger patients.

Black patients
There were too few black patients enrolled in the placebo-controlled studies with subcutaneous Benlysta to draw meaningful conclusions about the effects of race on clinical outcomes.

The safety and efficacy of Benlysta administered intravenously have been studied in black patients. The currently available data are described in the Summary of Product Characteristics of Benlysta 120 mg and 400 mg powder for concentrate for solution for infusion.

<u>Paediatric population</u>

<u>*SLE*</u>

Subcutaneous injection
Benlysta 200 mg solution for injection in the pre-filled syringe has not been evaluated in paediatric patients (see section 4.2). For Benlysta 200 mg solution for injection in the pre-filled pen, the safety and efficacy of Benlysta administered subcutaneously to paediatric patients 5 to < 18 years of age with active SLE is supported by a population pharmacokinetic model and simulation integrating data from an open-label pharmacokinetic study of 25 paediatric patients with active SLE administered Benlysta subcutaneously

(200908), and a study of paediatric patients with active SLE administered Benlysta intravenously (PLUTO) described below (see section 5.2).

Intravenous infusion
The safety and efficacy of Benlysta was evaluated in a randomised, double-blind, placebo-controlled, 52-week study (PLUTO) in 93 paediatric patients with a clinical diagnosis of SLE according to the ACR classification criteria. Patients had active SLE disease, defined as a SELENA-SLEDAI score ≥ 6 and positive autoantibodies at screening as described in the adult trials. Patients were on a stable SLE treatment regimen (standard of care) and had similar inclusion criteria as the adult studies. Patients who had severe active lupus nephritis, severe active CNS lupus, primary immunodeficiency, IgA deficiency or acute or chronic infections requiring management were excluded from the study. The study was conducted in the US, South America, Europe, and Asia. Patient median age was 15 years (range 6 to 17 years). In the 5- to 11-year-old-group (n = 13) the SELENA-SLEDAI score ranged from 4 to 13, and in 12- to 17-year-old-group (n = 79) the SELENA-SLEDAI score ranged from 4 to 20. The majority (94.6 %) of patients were female. The study was not powered for any statistical comparisons and all data are descriptive.

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 4).

Table 4. Paediatric response rate at Week 52

Response[1]	**Placebo (n = 40)**	**Benlysta 10 mg/kg (n = 53)**
SLE Responder Index (%)	43.6 (17/39)	52.8 (28/53)
Odds ratio (95 % CI) vs. placebo		1.49 (0.64, 3.46)
Components of SLE Responder Index		
Percent of patients with reduction in SELENA-SLEDAI ≥ 4 (%)	43.6 (17/39)	54.7 (29/53)
Odds ratio (95 % CI) vs. placebo		1.62 (0.69, 3.78)
Percent of patients with no worsening by BILAG index (%)	61.5 (24/39)	73.6 (39/53)
Odds ratio (95 % CI) vs. placebo		1.96 (0.77, 4.97)
Percent of patients with no worsening by PGA (%)	66.7 (26/39)	75.5 (40/53)
Odds ratio (95 % CI) vs. placebo		1.70 (0.66, 4.39)

[1] Analyses excluded any subject missing a baseline assessment for any of the components (1 for placebo).

Among patients experiencing a severe flare, the median study day of the first severe flare was Day 150 in the Benlysta group and Day 113 in the placebo group. Severe flares were observed in 17.0 % of the Benlysta group compared to 35.0 % of the placebo group over the 52 weeks of observation (observed treatment difference = 18.0 %; hazard ratio = 0.36, 95 % CI: 0.15, 0.86). 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 receiving Benlysta demonstrated improvement compared with placebo (Table 5).

Table 5. PRINTO/ACR response rate at Week 52

	Proportion of patients with at least 50 % improvement in any 2 of 5 components[1] and no more than one of the remaining worsening by more than 30 %		Proportion of patients with at least 30 % improvement in 3 of 5 components[1] 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)

[1] 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.

5.2 Pharmacokinetic properties

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 Benlysta subcutaneously.

Absorption

Benlysta in the pre-filled syringe is administered by subcutaneous injection.

Following subcutaneous administration, the bioavailability of belimumab was approximately 74 %. Steady-state exposure was reached after approximately 11 weeks of subcutaneous administration. The maximum serum concentration (C_{max}) of belimumab at steady state was 108 µg/mL.

Distribution

Belimumab was distributed to tissues with steady-state volume (Vss) of distribution of approximately 5 litres.

Biotransformation

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

Following subcutaneous administration, belimumab had a terminal half-life of 18.3 days. The systemic clearance was 204 mL/day.

Lupus nephritis study

A population pharmacokinetic analysis was conducted in 224 adult patients with lupus nephritis who received Benlysta 10 mg/kg body weight 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 belimumab 10 mg/kg body weight intravenously.

Based on population pharmacokinetic modelling and simulation, the steady-state average concentrations of subcutaneous administration of belimumab 200 mg once weekly in adults with lupus nephritis are predicted to be similar to those observed in adults with lupus nephritis receiving belimumab 10 mg/kg body weight intravenously every 4 weeks.

Special patient populations

Paediatric population: Benlysta 200 mg solution for injection in the pre-filled syringe has not been evaluated in paediatric patients (see section 4.2). For Benlysta 200 mg solution for injection in the pre-filled pen, the pharmacokinetic parameters of belimumab administered subcutaneously are based on a population pharmacokinetic analysis of 25 patients from a Phase II pharmacokinetic study in paediatric patients with SLE receiving belimumab subcutaneously and the Phase II study in paediatric patients with SLE receiving belimumab intravenously. Following subcutaneous administration of 200 mg of belimumab in paediatric patients 5 to less than 18 years of age [weekly (patients weighing ≥ 50 kg), every 10 days (patients weighing 30 to < 50 kg) or every 2 weeks (patients weighing 15 to < 30 kg)], the steady state average belimumab concentration is estimated to be similar to that of adult SLE subjects following subcutaneous administration of 200 mg belimumab weekly, and similar to that of paediatric SLE subjects following intravenous administration of belimumab 10 mg/kg body weight on Days 0, 14 and 28, and at 4-week intervals thereafter. Simulated steady-state geometric mean C_{max}, C_{avg}, C_{min}, and AUC (calculated over the dosing interval) are estimated to be 124 µg/mL, 119 µg/mL, 111 µg/mL and 834 day•µg/mL for paediatric patients weighing ≥ 50 kg receiving belimumab once weekly, 114 µg/mL, 105 µg/mL, 91 µg/mL and 1051 day•µg/mL for paediatric patients weighing 30 to < 50 kg receiving belimumab every 10 days, and 119 µg/mL, 103 µg/mL, 79 µg/mL and 1438 day•µg/mL for paediatric patients weighing 15 to < 30 kg receiving belimumab every 2 weeks.

Elderly: Benlysta has been studied in a limited number of elderly patients. Age did not affect belimumab exposure in the subcutaneous population pharmacokinetic analysis. However, given the small number of subjects ≥ 65, an effect of age cannot be ruled out conclusively.

Renal impairment: No specific studies have been conducted to examine the effects of renal impairment on the pharmacokinetics of belimumab. During clinical development, Benlysta was studied in a limited number of SLE patients with mild (creatinine clearance [CrCl] ≥ 60 and < 90 mL/min), moderate (CrCl ≥ 30 and < 60 mL/min), or severe (CrCl ≥ 15 and < 30 mL/min) renal impairment: 121 patients with mild renal impairment and 30 patients with moderate renal impairment received Benlysta subcutaneously; 770 patients with mild renal impairment, 261 patients with moderate renal impairment and 14 patients with severe renal impairment received Benlysta intravenously.

No clinically significant reduction in systemic clearance as a result of renal impairment was observed. Therefore, no dose adjustment is recommended for patients with renal impairment.

Hepatic impairment: No specific studies have been 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 and changes in hepatic function are unlikely to have any effect on the elimination of belimumab.

Body weight/Body mass index (BMI)

The effects of body weight and BMI on belimumab exposure after subcutaneous administration in adults were not considered clinically meaningful. There was no significant impact on efficacy and safety based on weight. Therefore, no dose adjustment in adults is recommended.

The effects of body weight on belimumab exposure after subcutaneous administration in paediatric patients have been determined using a population pharmacokinetic model. Paediatric patients with lower body weight

have lower belimumab clearance and volume of distribution resulting in increased exposure. To ensure belimumab exposures remain within acceptable limits and are consistent across the paediatric weight range, patients with lower body weight are dosed belimumab less frequently (see section 4.2).

Transitioning from intravenous to subcutaneous administration

SLE
Patients with SLE transitioning from 10 mg/kg body weight intravenously every 4 weeks to a 200 mg subcutaneous regimen 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). Based on simulations with population pharmacokinetic parameters the steady-state average belimumab concentrations for 200 mg subcutaneous every week (in adult patients, and in paediatric patients 5 to under 18 years of age and ≥ 50 kg), every 10 days (in paediatric patients 5 to under 18 years of age and 30 to < 50 kg) or every 2 weeks (in paediatric patients 5 to under 18 years of age and 15 to < 30 kg), were similar to 10 mg/kg body weight intravenous every 4 weeks.

Lupus nephritis
One to 2 weeks after completing the first 2 intravenous doses, patients with lupus nephritis transitioning from 10 mg/kg body weight intravenously to 200 mg subcutaneously weekly, are predicted to have average belimumab serum concentrations similar to patients dosed with 10 mg/kg body weight intravenously every 4 weeks based on population pharmacokinetic simulations (see section 4.2).

5.3 Preclinical safety data

Non-clinical data reveal 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 the 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 body weight by intravenous infusion (approximately 9 times the anticipated maximum human clinical exposure) every 2 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 3 months of life in infant monkeys; IgM levels in infants exposed to belimumab *in utero* recovered by 6 months of age.

Effects on male and female fertility in monkeys were assessed in the 6-month repeat dose toxicology studies of belimumab at doses up to and including 50 mg/kg body weight. No treatment-related changes were noted in the male and female reproductive organs of sexually mature animals. An informal assessment of menstrual cycling in females demonstrated no belimumab-related changes.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Arginine hydrochloride
Histidine
Histidine monohydrochloride
Polysorbate 80 (E 433)

Sodium chloride
Water for injection

6.2 Incompatibilities

None known.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in a refrigerator (2 °C to 8 °C).
Do not freeze.
Store in the original carton in order to protect from light.

A single Benlysta pre-filled syringe can be stored at temperatures up to a maximum of 25 °C for a period of up to 12 hours. The pre-filled syringe must be protected from light, and discarded if not used within the 12 hour period.

6.5 Nature and contents of container

1 mL solution in a type 1 glass syringe with a fixed needle (stainless steel) and needle cap.

Available in pack of 1 pre-filled syringe and pack of 4 pre-filled syringes.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Comprehensive instructions for subcutaneous administration of Benlysta in a pre-filled syringe are provided at the end of the package leaflet (see Step-by-step instructions).

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

7. MARKETING AUTHORISATION HOLDER

GlaxoSmithKline (Ireland) Limited
12 Riverwalk
Citywest Business Campus
Dublin 24
Ireland

8. MARKETING AUTHORISATION NUMBERS

EU/1/11/700/006 1 pre-filled syringe
EU/1/11/700/007 4 pre-filled syringes

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 13 July 2011
Date of latest renewal: 18 February 2016

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Benlysta 120 mg powder for concentrate for solution for infusion.
Benlysta 400 mg powder for concentrate for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Benlysta 120 mg powder for concentrate for solution for infusion.

Each vial contains 120 mg of belimumab. After reconstitution, the solution contains 80 mg belimumab per mL.

Benlysta 400 mg powder for concentrate for solution for infusion.

Each vial contains 400 mg of belimumab. After reconstitution, the solution contains 80 mg belimumab per mL.

Belimumab is a human, IgG1λ monoclonal antibody, produced in a mammalian cell line (NS0) by recombinant DNA technology.

Excipient with known effect

Benlysta 120 mg powder for concentrate for solution for infusion.

Each vial contains 0.6 mg polysorbate 80.

Benlysta 400 mg powder for concentrate for solution for infusion.

Each vial contains 2.0 mg polysorbate 80.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion.
White to off-white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Benlysta is indicated as add-on therapy in patients aged 5 years and older with active, autoantibody-positive systemic lupus erythematosus (SLE) with a high degree of disease activity (e.g., positive anti-dsDNA and low complement) despite standard therapy (see section 5.1).

Benlysta is indicated in combination with background immunosuppressive therapies for the treatment of adult patients with active lupus nephritis (see sections 4.2 and 5.1).

4.2 Posology and method of administration

Benlysta treatment should be initiated and supervised by a qualified physician experienced in the diagnosis and treatment of SLE. Benlysta infusions must be administered by a qualified healthcare professional trained to give infusion therapy.

Administration of Benlysta may result in severe or life-threatening hypersensitivity reactions and infusion reactions. Patients have been reported to develop symptoms of acute hypersensitivity several hours after the infusion has been administered. Recurrence of clinically significant reactions after initial appropriate treatment of symptoms has also been observed (see sections 4.4 and 4.8). Therefore, Benlysta must be administered in an environment where resources for managing such reactions are immediately available. It is recommended that patients remain under clinical supervision for a prolonged period of time (for several hours), following at least the first 2 infusions, taking into account the possibility of a late onset reaction.

Patients treated with Benlysta must be made aware of the potential risk of severe or life-threatening hypersensitivity and the potential for delayed onset or recurrence of symptoms. The package leaflet must be provided to the patient each time Benlysta is administered (see section 4.4).

Posology

Premedication including an antihistamine, with or without an antipyretic, may be administered before the infusion of Benlysta (see section 4.4).

In patients with SLE or active lupus nephritis, the recommended Benlysta dose regimen is 10 mg/kg body weight on Days 0, 14 and 28, and at 4-week intervals thereafter. The patient's condition should be evaluated continuously.

In patients with SLE, discontinuation of treatment with Benlysta is to be considered if there is no improvement in disease control after 6 months of treatment.

In patients with active lupus nephritis, Benlysta is to be used in combination with corticosteroids and mycophenolate or cyclophosphamide for induction, or mycophenolate or azathioprine for maintenance.

Transition from intravenous to subcutaneous administration

SLE
If a patient with SLE is being transitioned from Benlysta intravenous administration to subcutaneous administration, the first subcutaneous injection must be administered 1 to 4 weeks after the last intravenous dose (see section 5.2).

Lupus nephritis
If a patient with lupus nephritis is being transitioned from Benlysta intravenous administration to subcutaneous administration, it is recommended that the first dose of 200 mg subcutaneous injection be administered 1 to 2 weeks after the last intravenous dose. This transition can occur any time after the patient completes the first 2 intravenous doses (see section 5.2).

Special populations

Elderly

Data on patients ≥ 65 years are limited (see section 5.1). Benlysta should be used with caution in the elderly. Dose adjustment is not required (see section 5.2).

Renal impairment

Belimumab has been studied in a limited number of SLE patients with renal impairment.

On the basis of the available information, dose 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 lack of data (see section 5.2).

Hepatic impairment

No specific studies with Benlysta have been conducted in patients with hepatic impairment. Patients with hepatic impairment are unlikely to require dose adjustment (see section 5.2).

Paediatric population

SLE
The recommended Benlysta dose regimen for children 5 years of age and older is 10 mg/kg body weight on Days 0, 14 and 28, and at 4-week intervals thereafter.

The safety and efficacy of Benlysta intravenous administration in children under 5 years of age have not been established. No data are available.

Lupus nephritis
The safety and efficacy of Benlysta intravenous administration in children and adolescents under 18 years of age have not been established. No data are available.

Method of administration

Benlysta is administered intravenously by infusion, and must be reconstituted and diluted before administration. For instructions on reconstitution, dilution, and storage of the medicinal product before administration, see section 6.6.

Benlysta must be infused over a 1-hour period.

Benlysta must not be administered as an intravenous 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 sections 4.4 and 4.8).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

In order to improve traceability of biological medicinal products, the tradename and the batch number of the administered product should be clearly recorded.

Benlysta has not been studied in the following adult and paediatric patient groups, and is not recommended in:

- severe active central nervous system lupus (see section 5.1)
- 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

Available data do not support the co-administration of rituximab with Benlysta in patients with SLE (see section 5.1). Caution needs to be exercised if Benlysta is co-administered with other B cell targeted therapy.

Infusion reactions and hypersensitivity

Administration of Benlysta may result in hypersensitivity reactions and infusion reactions which can be severe, and fatal. In the event of a severe reaction, Benlysta administration must be interrupted and appropriate medical therapy administered (see section 4.2). The risk of hypersensitivity reactions is greatest with the first two infusions; however the risk must be considered for every infusion administered. Patients with a history of multiple drug allergies or significant hypersensitivity may be at increased risk.

Premedication including an antihistamine, with or without an antipyretic, may be administered before the infusion of Benlysta. There is insufficient knowledge to determine whether premedication could diminish the frequency or severity of infusion reactions.

In clinical studies, serious infusion and hypersensitivity reactions affected approximately 0.9 % of adult patients, and included anaphylactic reaction, bradycardia, hypotension, angioedema, and dyspnoea. Infusion reactions occurred more frequently during the first two infusions and tended to decrease with subsequent infusions (see section 4.8). Patients have been reported to develop symptoms of acute hypersensitivity several hours after the infusion has been administered. Recurrence of clinically significant reactions after initial appropriate treatment of symptoms has also been observed (see sections 4.2 and 4.8). Therefore, Benlysta must be administered in an environment where resources for managing such reactions are immediately available. It is recommended that patients remain under clinical supervision for a prolonged period of time (for several hours), following at least the first 2 infusions, taking into account the possibility of a late onset reaction. Patients must be advised that hypersensitivity reactions are possible, on the day of, or several days after infusion, and be informed of potential signs and symptoms and the possibility of recurrence. Patients must be instructed to seek immediate medical attention if they experience any of these symptoms. The package leaflet must be provided to the patient each time Benlysta is administered (see section 4.2).

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

Infections

The mechanism of action of belimumab could increase the risk for the development of infections in adults and children with lupus, including opportunistic infections, and younger children may be at increased risk. In controlled clinical studies, the incidence of serious infections was similar across the Benlysta and placebo groups; however, fatal infections (e.g. pneumonia and sepsis) occurred more frequently in patients receiving Benlysta compared with placebo (see section 4.8). Pneumococcal vaccination should be considered before initiating Benlysta treatment. Benlysta must not be initiated in patients with active serious infections (including serious chronic infections). Physicians need to exercise caution and carefully assess if the benefits are expected to outweigh the risks when considering the use of Benlysta in patients with a history of recurrent infection. Physicians need to advise patients to contact their health care provider if they develop symptoms of an infection. Patients who develop an infection while undergoing treatment with Benlysta must be monitored closely and careful consideration given to interrupting immunosuppressant therapy including Benlysta until the infection is resolved. The risk of using Benlysta in patients with active or latent tuberculosis is unknown.

Depression and suicidality

In controlled clinical intravenous and subcutaneous studies, psychiatric disorders (depression, suicidal ideation and behaviour including suicides) have been reported more frequently in patients receiving Benlysta (see section 4.8). Physicians should 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 must advise patients (and caregivers where appropriate) to contact their health care provider about new or worsening psychiatric symptoms. In patients who experience such symptoms, treatment discontinuation is to be considered.

Severe cutaneous adverse reactions

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), which can be life-threatening or fatal, have been reported in association with Benlysta treatment. Patients should be advised of the signs and symptoms of SJS and TEN and monitored closely for skin reactions. If signs and symptoms suggestive of these reactions appear, Benlysta should be withdrawn immediately, and an alternative treatment should be considered. If the patient has developed SJS or TEN with the use of Benlysta, treatment with Benlysta must not be restarted in this patient at any time.

Progressive multifocal leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) has been reported with Benlysta treatment for SLE. Physicians must be particularly alert to symptoms suggestive of PML that patients may not notice (e.g., cognitive, neurological or psychiatric symptoms or signs). Patients should be monitored for any of these new or worsening symptoms or signs, and if such symptoms/signs occur, referral to a neurologist and appropriate diagnostic measures for PML must be considered as clinically indicated. If PML is suspected, immunosuppressant therapy, including Benlysta, must be suspended until PML has been excluded. If PML is confirmed, immunosuppressant therapy, including Benlysta, must be discontinued.

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, belimumab may interfere with the response to immunisations. However, in a small 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 receiving standard immunosuppressive treatment at the time of vaccination. There are insufficient data to draw conclusions regarding response to other vaccines.

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. In a substudy, a small group of patients who had previously received either tetanus, pneumococcal or influenza vaccinations were found to maintain protective titres after treatment with Benlysta.

Malignancies and lymphoproliferative disorders

Immunomodulatory medicinal products, including Benlysta, may increase the risk of malignancy. Caution is advised when considering Benlysta therapy for patients with a history of malignancy or when considering continuing treatment in patients who develop malignancy. Patients with malignant neoplasm within the last 5 years have not been studied, with the exception of those with basal or squamous cell cancers of the skin, or cancer of the uterine cervix, that has been fully excised or adequately treated.

Polysorbate 80 content

This medicinal product contains polysorbate 80 (see section 2), which may cause allergic reactions.

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially 'sodium-free'. However, as Benlysta powder for concentrate is diluted in a solution for infusion that contains sodium, this is to be taken into consideration for patients on a controlled sodium diet (see section 6.6).

4.5 Interaction with other medicinal products and other forms of interaction

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 is to be considered for patients being treated with CYP substrates with a narrow therapeutic index, where the dose is individually adjusted (e.g. warfarin).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

Women of childbearing potential must use effective contraception during Benlysta treatment and for at least 4 months after the last treatment.

Pregnancy

There are a limited amount of data from the use of Benlysta in pregnant women. Besides an expected pharmacological effect i.e. reduction of B cells, animal studies in monkeys do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). Benlysta should not be used during pregnancy unless the potential benefit justifies the potential risk to the foetus.

Breast-feeding

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 monkeys administered 150 mg/kg body weight every 2 weeks.

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

Fertility

There are no data on the effects of belimumab on human fertility. Effects on male and female fertility have not been formally evaluated in animal studies (see section 5.3).

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. No detrimental effects on such activities are predicted from the pharmacology of belimumab. It is recommended that the clinical status of the subject and the adverse reaction profile of Benlysta be borne in mind when considering the patient's ability to perform tasks that require judgement, motor or cognitive skills.

4.8 Undesirable effects

Summary of the safety profile in adults

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

The data presented in the table below reflect exposure in 674 patients from the three pre-registration clinical studies and 470 patients in the subsequent placebo-controlled study with SLE administered Benlysta intravenously (10 mg/kg body weight over a 1-hour period on Days 0, 14, 28, and then every 28 days for up to 52 weeks), and 556 patients with SLE exposed to 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 body weight 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 medicinal products, anti-malarials, non-steroidal anti-inflammatory medicinal products.

Adverse reactions were reported in 84 % of Benlysta-treated patients and 87 % of placebo-treated patients. The most frequently reported adverse reaction (≥ 5 % of patients with SLE treated with Benlysta plus standard of care and at a rate ≥ 1 % greater than placebo) was nasopharyngitis. The proportion of patients who discontinued treatment due to adverse reactions was 7 % for Benlysta-treated patients and 8 % for placebo-treated patients.

The most frequently reported adverse reactions (> 5 % of patients with active lupus nephritis treated with Benlysta plus standard of care) were upper respiratory tract infection, urinary tract infection, and herpes zoster. The proportion of patients who discontinued treatment due to adverse reactions was 12.9 % for Benlysta-treated patients and 12.9 % for placebo-treated patients.

Severe cutaneous adverse reactions: Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported in association with Benlysta treatment (see section 4.4).

Tabulated list of adverse reactions

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

Very common	≥ 1/10
Common	≥ 1/100 to < 1/10
Uncommon	≥ 1/1000 to < 1/100
Rare	≥ 1/10 000 to < 1/1000
Not known	cannot be estimated from the available data.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. The frequency given is the highest seen with either formulation.

System organ class	Frequency	Adverse reactions
Infections and infestations[1]	Very common	Bacterial infections, e.g. bronchitis, urinary tract infection
	Common	Gastroenteritis viral, pharyngitis, nasopharyngitis, viral upper respiratory tract infection
Blood and lymphatic system disorders	Common	Leucopenia
Immune system disorders	Common	Hypersensitivity reactions[2]
	Uncommon	Anaphylactic reaction
	Rare	Delayed-type, non-acute hypersensitivity reactions
Psychiatric disorders	Common	Depression
	Uncommon	Suicidal behaviour, suicidal ideation
Nervous system disorders	Common	Migraine
Gastrointestinal disorders	Common	Diarrhoea, nausea
Skin and subcutaneous tissue disorders	Common	Injection site reactions[3], urticaria, rash
	Uncommon	Angioedema
	Not known	Stevens-Johnson syndrome, toxic epidermal necrolysis
Musculoskeletal and connective tissue disorders	Common	Pain in extremity
General disorders and administration site conditions	Common	Infusion or injection-related systemic reactions[2], pyrexia

[1] See 'Description of selected adverse reactions' and section 4.4 'Infections' for further information.
[2] '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.
[3] Applies to subcutaneous formulation only.

Description of selected adverse reactions

Data presented below are pooled from the three pre-registration intravenous clinical studies (10 mg/kg body weight intravenous dose only) and the subcutaneous clinical study. 'Infections' and 'Psychiatric disorders' also include data from a post-marketing study.

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.

Infections: The overall incidence of infections in intravenous and subcutaneous pre-registration SLE studies was 63 % in both groups receiving Benlysta or placebo. Infections occurring in at least 3 % of patients receiving Benlysta and at least 1 % more frequently than patients receiving placebo were viral upper respiratory tract infection, bronchitis, and urinary tract infection bacterial. Serious infections occurred in 5 % of patients in both groups receiving Benlysta or placebo*;* serious opportunistic infections accounted for 0.4 % and 0 % of these, respectively. Infections leading to discontinuation of treatment occurred in 0.7 % of patients receiving Benlysta and 1.5 % of patients receiving placebo. Some infections were severe or fatal.

For information on infections observed in paediatric patients with SLE see Paediatric population section below.

In the lupus nephritis study, patients were receiving a background of standard therapy (see section 5.1) 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.

In a randomised, double-blind, 52-week, post-marketing safety SLE study (BEL115467) which assessed mortality and specific adverse events in adults, serious infections occurred in 3.7 % of patients receiving Benlysta (10 mg/kg body weight intravenously) vs. 4.1 % of patients receiving placebo. However, fatal infections (e.g. pneumonia and sepsis) occurred in 0.45 % (9/2002) of Benlysta-treated patients vs. 0.15 % (3/2001) of patients receiving placebo, while the incidence of all-cause mortality was 0.50 % (10/2002) vs. 0.40 % (8/2001), respectively. Most fatal infections were observed during the first 20 weeks of treatment with Benlysta.

Psychiatric disorders: In the pre-registration intravenous SLE clinical studies, serious psychiatric events were reported in 1.2 % (8/674) of patients receiving Benlysta 10 mg/kg body weight 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 body weight and 0.3 % (2/675) of patients receiving placebo. There were two suicides in Benlysta-treated patients (including one receiving Benlysta 1 mg/kg body weight).

In a 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) of patients receiving placebo. The overall incidence of serious suicidal ideation or behaviour or self-injury without suicidal intent was 0.7 % (15/2002) in patients receiving Benlysta and 0.2 % (5/2001) in the placebo group. No suicide was reported in either group.

The intravenous SLE studies above 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.

Leucopenia: The incidence of leucopenia reported in patients with SLE as an adverse event was 3 % in the group receiving Benlysta and 2 % in the group receiving placebo.

Gastrointestinal disorders: Obese patients [Body mass index (BMI) > 30 kg/m^2] with SLE treated with intravenously administered Benlysta reported higher rates of nausea, vomiting and diarrhoea relative to placebo, and compared with normal-weight patients (BMI ≥ 18.5 to ≤ 30 kg/m^2). None of these gastrointestinal events in obese patients were serious.

Paediatric population

The adverse reaction profile in paediatric patients is based on one subcutaneous study and one intravenous study.

In a 52-week open-label study in which 25 paediatric patients (10 to 17 years of age) with SLE received subcutaneous Benlysta at a comparable exposure to adults (200 mg at a set dosing interval based on body weight), on a background of concomitant treatments, the safety profile in paediatric patients receiving Benlysta subcutaneously was consistent with the known safety profile for belimumab.

In a 52-week placebo-controlled study in which 53 patients (6 to 17 years of age) with SLE received Benlysta (10 mg/kg body weight intravenously on Days 0, 14, 28, and then every 28 days, on a background of concomitant treatments), no new safety signals were observed in the paediatric population 12 years of age and above (n = 43). Safety data in children younger than 12 years of age (n = 10) are limited.

Infections
5- to 11-year-old group: infections were reported in 8/10 patients receiving Benlysta intravenously and 3/3 patients receiving placebo, and serious infections were reported in 1/10 patients receiving Benlysta intravenously and 2/3 patients receiving placebo (see section 4.4).
12- to 17-year-old group: infections were reported in 22/43 patients receiving Benlysta intravenously and 25/37 patients receiving placebo, and serious infections were reported in 3/43 patients receiving Benlysta intravenously and 3/37 patients receiving placebo. In the open-label extension phase there was one fatal infection in a patient receiving Benlysta intravenously.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via the national reporting system listed in Appendix V.

4.9 Overdose

There is limited clinical experience with overdose 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 body weight 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 body weight.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, monoclonal antibodies, ATC code: L04AG04

Mechanism of action

Belimumab is a human IgG1λ monoclonal antibody specific for soluble human B Lymphocyte Stimulator protein (BLyS, also referred to as BAFF and TNFSF13B). Belimumab blocks the binding of soluble BLyS, a B cell survival factor, to its receptors on B cells. 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.

BLyS levels are elevated in patients with SLE and other autoimmune diseases. There is an association between plasma BLyS levels and SLE disease activity. The relative contribution of BLyS levels to the pathophysiology of SLE is not fully understood.

Pharmacodynamic effects

Changes in biomarkers were seen in clinical trials with Benlysta administered intravenously. In adult patients with SLE with hypergammaglobulinemia, normalization of IgG levels was observed by Week 52 in 49 % and 20 % of patients receiving Benlysta and placebo, respectively.

In patients with SLE with anti-dsDNA antibodies, 16 % of patients treated with Benlysta converted to anti-dsDNA negative compared with 7 % of the patients receiving placebo by Week 52.

In patients with SLE with low complement levels, normalization of C3 and C4 was observed by Week 52 in 38 % and 44 % of patients receiving Benlysta and in 17 % and 18 % of patients receiving placebo, respectively.

Of the anti-phospholipid antibodies, only anti-cardiolipin antibody was measured. For anti-cardiolipin IgA antibody a 37 % reduction at Week 52 was seen ($p = 0.0003$), for anti-cardiolipin IgG antibody a 26 % reduction at Week 52 was seen ($p = 0.0324$) and for anti-cardiolipin IgM a 25 % reduction was seen ($p = NS$, 0.46).

Changes in B cells (including naïve, memory and activated B cells, and plasma cells) and IgG levels occurring in patients with SLE during ongoing treatment with intravenous belimumab were followed in a long-term uncontrolled extension study. After 7 and a half years of treatment (including the 72-week parent study), a substantial and sustained decrease in various B cell subsets was observed leading to 87 % median reduction in naïve B cells, 67 % in memory B cells, 99 % in activated B cells, and 92 % median reduction 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 Benlysta (10 mg/kg body weight intravenously) 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 Benlysta group as expected with the known mechanism of belimumab. At Week 104, the median percent increase from baseline in IgG was 17 % for Benlysta 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 one intravenous study in paediatric patients with SLE (6 to 17 years of age) the pharmacodynamic response was consistent with the adult data.

Immunogenicity

Assay sensitivity for neutralising antibodies and non-specific anti-drug antibody (ADA) is limited by the presence of active drug in the collected samples. The true occurrence of neutralising antibodies and non-specific anti-drug antibody in the study population is therefore not known. In the two Phase III SLE studies in adults, 4 of the 563 (0.7 %) patients in the 10 mg/kg body weight group and 27 out of 559 (4.8 %) patients in the 1 mg/kg body weight group tested positive for persistent presence of anti-belimumab

antibodies. Among persistent-positive subjects in the Phase III SLE studies, 1/10 (10 %), 2/27 (7 %) and 1/4 (25 %) subjects in the placebo, 1 mg/kg body weight and 10 mg/kg body weight groups, respectively, experienced infusion reactions on a dosing day; these infusion reactions were all non-serious and mild to moderate in severity. Few patients with ADA reported serious/severe AEs. The rates of infusion reactions among persistent-positive subjects were comparable to the rates for ADA negative patients of 75/552 (14 %), 78/523 (15 %), and 83/559 (15 %) in the placebo, 1 mg/kg body weight and 10 mg/kg body weight groups, respectively.

In the lupus nephritis study where 224 adult patients received Benlysta 10 mg/kg body weight intravenously, no anti-belimumab antibodies were detected.

In one intravenous study in 6- to 17-year-old paediatric patients with SLE (n = 53), none of the patients developed anti-belimumab antibodies.

Clinical efficacy and safety

SLE

Intravenous infusion in adults
The efficacy of Benlysta administered intravenously was evaluated in 2 randomised, double-blind, placebo-controlled studies in 1684 patients with a clinical diagnosis of SLE according to the American College of Rheumatology (ACR) classification criteria. Patients had active SLE disease, defined as a SELENA-SLEDAI (SELENA = Safety of Estrogens in Systemic Lupus Erythematosus National Assessment; SLEDAI = Systemic Lupus Erythematosus Disease Activity Index) score ≥ 6 and positive anti-nuclear antibody (ANA) 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 consisting of (alone or in combination): corticosteroids, anti-malarials, NSAIDs or other immunosuppressives. The two studies were similar in design except that BLISS-76 was a 76-week study and BLISS-52 was a 52-week study. In both studies the primary efficacy endpoint was evaluated at 52 weeks.

Patients who had severe active lupus nephritis and patients who had severe active central nervous system (CNS) lupus were excluded.

BLISS-76 was conducted primarily in North America and Western Europe. Background medicinal products included corticosteroids (76 %; > 7.5 mg/day 46 %), immunosuppressives (56 %), and anti-malarials (63 %).

BLISS-52 was conducted in South America, Eastern Europe, Asia, and Australia. Background medicinal products included corticosteroids (96 %; > 7.5 mg/day 69 %), immunosuppressives (42 %), and anti-malarials (67 %).

At baseline 52 % of patients had high disease activity (SELENA SLEDAI score ≥ 10), 59 % of patients had mucocutaneous, 60 % had musculoskeletal, 16 % had haematological, 11 % had renal and 9 % had vascular organ domain involvement (BILAG A or B at baseline).

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 measures improvement in SLE disease activity, without worsening in any organ system, or in the patient's overall condition.

Table 1. Response rate at Week 52

Response	BLISS-76		BLISS-52		BLISS-76 and BLISS-52 pooled	
	Placebo[1] (n = 275)	Benlysta 10 mg/kg[1] (n = 273)	Placebo[1] (n = 287)	Benlysta 10 mg/kg[1] (n = 290)	Placebo[1] (n = 562)	Benlysta 10 mg/kg[1] (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)
Observed difference vs. placebo		9.4 %		14.0 %		11.8 %
Odds ratio (95 % CI) vs. placebo		1.52 (1.07, 2.15)		1.83 (1.30, 2.59)		1.68 (1.32, 2.15)
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)

[1] All patients received standard therapy

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 % to a dose equivalent to prednisone ≤ 7.5 mg/day during Weeks 40 through 52, was 17.9 % in the group receiving Benlysta and 12.3 % in the group receiving placebo (p = 0.0451).

Flares in SLE were defined by the modified SELENA SLEDAI SLE Flare Index. The median time to the first flare was delayed in the pooled group receiving Benlysta compared to the group receiving placebo (110 vs. 84 days, hazard ratio = 0.84, p = 0.012). Severe flares were observed in 15.6 % of the Benlysta group compared to 23.7 % of the placebo group over the 52 weeks of observation (observed treatment difference = -8.1 %; hazard ratio = 0.64, p = 0.0011).

Benlysta demonstrated improvement in fatigue compared with placebo measured by the FACIT-Fatigue scale in the pooled analysis. The mean change of score at Week 52 from baseline is significantly greater with Benlysta compared to placebo (4.70 vs. 2.46, p = 0.0006).

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

Post-hoc analysis has identified high responding subgroups such 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 ≥ 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[1] (%) 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

[1] Among patients with baseline prednisone dose > 7.5 mg/day.

The efficacy and safety of Benlysta in combination with a single cycle of rituximab have been studied in a Phase III, randomised, double-blind, placebo-controlled 104-week study including 292 patients (BLISS-BELIEVE). The primary endpoint was the proportion of subjects with a state of disease control defined as a SLEDAI-2K score ≤ 2, achieved without immunosuppressants and with corticosteroids at a prednisone equivalent dose of ≤ 5 mg/day at Week 52. This was achieved in 19.4 % (n = 28/144) of the patients treated with Benlysta in combination with rituximab and in 16.7 % (n = 12/72) of the patients treated with Benlysta in combination with placebo (odds ratio 1.27; 95 % CI: 0.60, 2.71; p = 0.5342). A higher frequency of adverse events (91.7 % vs. 87.5 %), serious adverse events (22.2 % vs. 13.9 %) and serious infections (9.0 % vs. 2.8 %) were observed in patients treated with Benlysta in combination with rituximab as compared to Benlysta in combination with placebo.

Lupus nephritis

In the intravenous SLE studies, described above, patients who had severe active lupus nephritis were excluded; however, 11 % of patients had renal organ domain involvement at baseline (based on BILAG A or B assessment). The following study in active lupus nephritis has been conducted.

The efficacy and safety of Benlysta 10 mg/kg body weight 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. Standard therapy included corticosteroids, 0 to 3 intravenous administrations of methylprednisolone (500 to1000 mg per administration), followed by oral prednisone 0.5 to 1 mg/kg/day with a total daily dose ≤60 mg/day and tapered to ≤ 10 mg/day by Week 24, with:

- mycophenolate mofetil 1 to 3 g/day orally or mycophenolate sodium 720 to 2160 mg/day orally for induction and maintenance, or
- cyclophosphamide 500 mg intravenously every 2 weeks for 6 infusions for induction followed by azathioprine orally at a target dose of 2 mg/kg/day 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 %) 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) ≤ 700 mg/g (79.5 mg/mmol) and estimated glomerular filtration rate (eGFR) ≥ 60 mL/min/1.73 m^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 < 500 mg/g (56.8 mg/mmol) and eGFR ≥ 90 mL/min/1.73 m^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 Benlysta 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 ≤ 700 mg/g (79.5 mg/mmol)	33.6 %	44.4 %	10.8 %	OR 1.54 (1.04, 2.29)	0.0320
eGFR≥ 60 mL/min/1.73 m^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 < 500 mg/g (56.8 mg/mmol)	28.7 %	39.5 %	10.8 %	OR 1.58 (1.05, 2.38)	0.0268
eGFR≥ 90 mL/min/1.73 m^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)]			-	HR 0.51 (0.34, 0.77)	0.0014

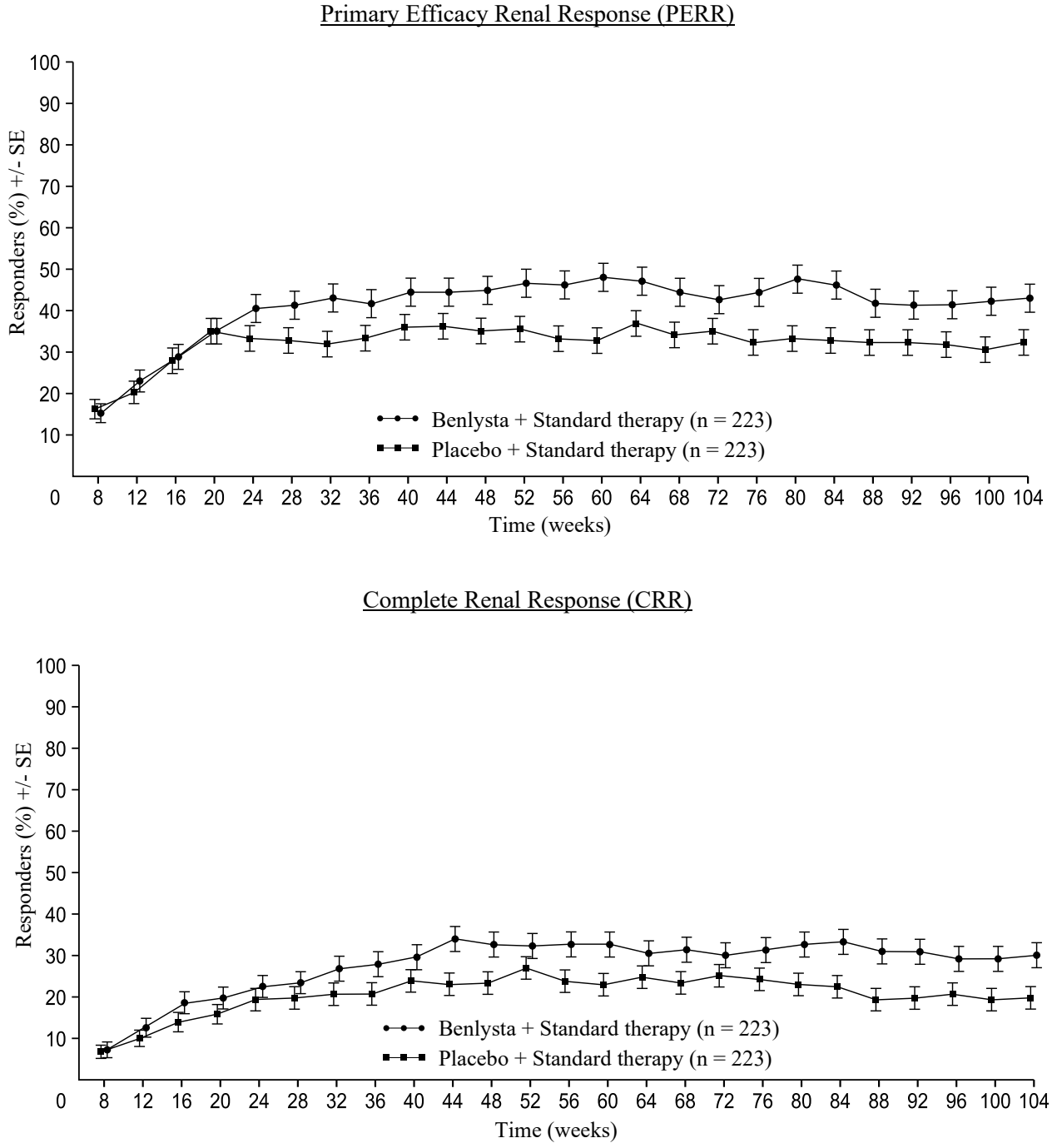
[1] PERR at Week 104 was the primary efficacy analysis; CRR at Week 104, PERR at Week 52 and time to renal-related event or death were included in the pre-specified testing hierarchy.

[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.

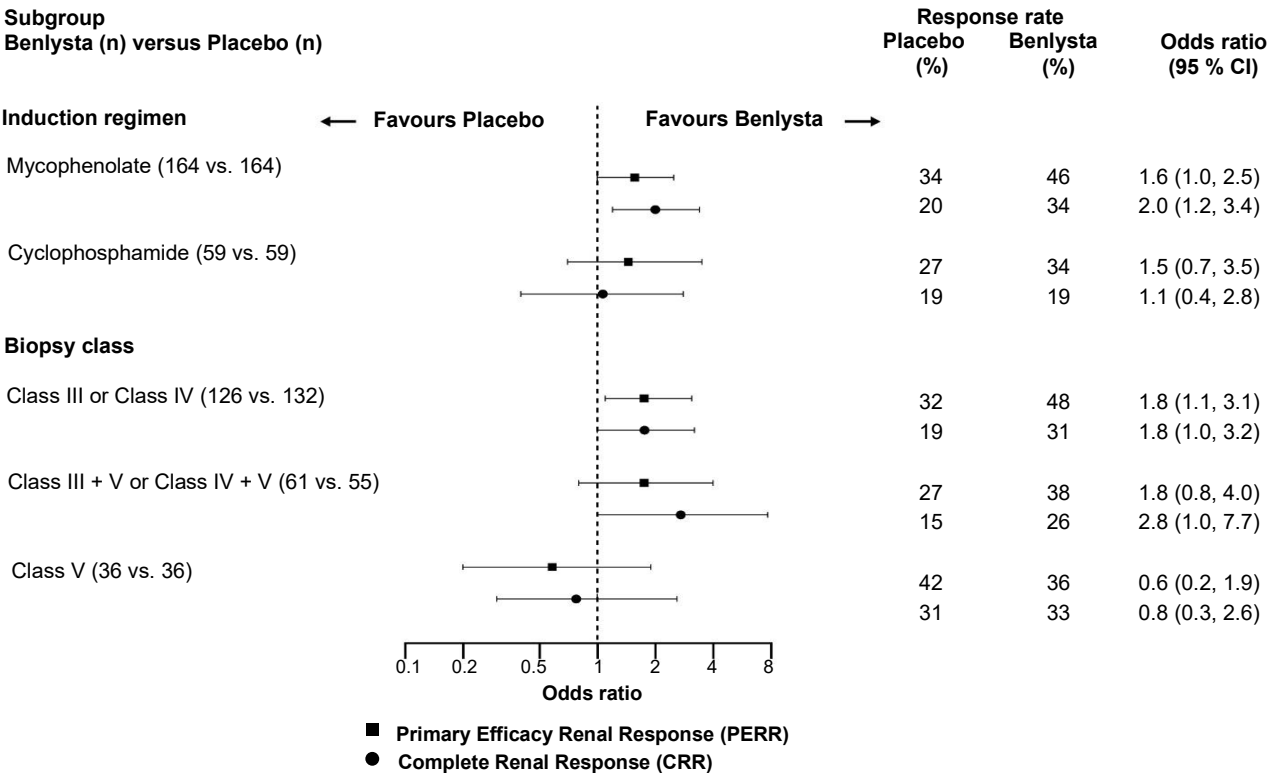
A numerically greater percentage of patients receiving Benlysta achieved PERR beginning at Week 24 compared with placebo, and this treatment difference was maintained through to Week 104. Beginning at Week 12, a numerically greater percentage of patients receiving Benlysta achieved CRR compared with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

Figure 1. Response rates in adults with lupus nephritis by visit



In descriptive subgroup analyses, key efficacy endpoints (PERR and CRR) were examined by induction regimen (mycophenolate or cyclophosphamide) and biopsy class (Class III or IV, Class III + V or Class IV + V, or Class V) (Figure 2).

Figure 2. Odds ratio of PERR and CRR at Week 104 across subgroups



<u>*Age and race*</u>

Age
There were no observed differences in efficacy or safety in SLE patients ≥ 65 years who received Benlysta intravenously or subcutaneously compared to the overall population in placebo-controlled studies; however, the number of patients aged ≥ 65 years (62 patients for efficacy and 219 for safety) is not sufficient to determine whether they respond differently to younger patients.

Black patients
Benlysta was administered intravenously to black patients with SLE in a randomised (2:1), double-blind, placebo-controlled, 52-week Phase III/IV study (EMBRACE). Efficacy was evaluated in 448 patients. 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. However, consistent with results from other studies, in black 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 body weight compared with 24.0 % for placebo (odds ratio 3.00; 95 % CI: 1.35, 6.68).

<u>Paediatric population</u>

<u>*SLE*</u>

The safety and efficacy of Benlysta was evaluated in a randomised, double-blind, placebo-controlled, 52-week study (PLUTO) in 93 paediatric patients with a clinical diagnosis of SLE according to the ACR classification criteria. Patients had active SLE disease, defined as a SELENA-SLEDAI score ≥ 6 and positive autoantibodies at screening as described in the adult trials. Patients were on a stable SLE treatment regimen (standard of care) and had similar inclusion criteria as the adult studies. Patients who had severe active lupus nephritis, severe active CNS lupus, primary immunodeficiency, IgA deficiency or acute or chronic infections requiring management were excluded from the study. The study was conducted in the US, South America,

Europe, and Asia. Patient median age was 15 years (range 6 to 17 years). In the 5- to 11-year-old-group (n = 13) the SELENA-SLEDAI score ranged from 4 to 13, and in 12- to 17-year-old-group (n = 79) the SELENA-SLEDAI score ranged from 4 to 20. The majority (94.6 %) of patients were female. The study was not powered for any statistical comparisons and all data are descriptive.

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 4).

Table 4. Paediatric response rate at Week 52

Response[1]	**Placebo (n = 40)**	**Benlysta 10 mg/kg (n = 53)**
SLE Responder Index (%)	43.6 (17/39)	52.8 (28/53)
Odds ratio (95 % CI) vs. placebo		1.49 (0.64, 3.46)
Components of SLE Responder Index		
Percent of patients with reduction in SELENA-SLEDAI ≥ 4 (%)	43.6 (17/39)	54.7 (29/53)
Odds ratio (95 % CI) vs. placebo		1.62 (0.69, 3.78)
Percent of patients with no worsening by BILAG index (%)	61.5 (24/39)	73.6 (39/53)
Odds ratio (95 % CI) vs. placebo		1.96 (0.77, 4.97)
Percent of patients with no worsening by PGA (%)	66.7 (26/39)	75.5 (40/53)
Odds ratio (95 % CI) vs. placebo		1.70 (0.66, 4.39)

[1] Analyses excluded any subject missing a baseline assessment for any of the components (1 for placebo).

Among patients experiencing a severe flare, the median study day of the first severe flare was Day 150 in the Benlysta group and Day 113 in the placebo group. Severe flares were observed in 17.0 % of the Benlysta group compared to 35.0 % of the placebo group over the 52 weeks of observation (observed treatment difference = 18.0 %; hazard ratio = 0.36, 95 % CI: 0.15, 0.86). 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 receiving Benlysta demonstrated improvement compared with placebo (Table 5).

Table 5. PRINTO/ACR response rate at Week 52

	Proportion of patients with at least 50 % improvement in any 2 of 5 components[1] and no more than one of the remaining worsening by more than 30 %		Proportion of patients with at least 30 % improvement in 3 of 5 components[1] 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)

[1] 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.

5.2 Pharmacokinetic properties

The intravenous pharmacokinetic parameters quoted below are based on population parameter estimates for the 563 patients with SLE who received Benlysta 10 mg/kg body weight in the two Phase III studies.

Absorption

Benlysta 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 µg/mL (range: 173-573 µg/mL) based on simulating the concentration time profile using the typical parameter values of the population pharmacokinetic model.

Distribution

Belimumab was distributed to tissues with steady-state volume (Vss) of distribution of approximately 5 litres.

Biotransformation

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 **(**range: 69-622 mL/day).

Lupus nephritis study

A population pharmacokinetic analysis was conducted in 224 adult patients with lupus nephritis who received Benlysta 10 mg/kg body weight 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 body weight intravenously.

Special patient populations

Paediatric population: The pharmacokinetic parameters are based on individual parameter estimates from a population pharmacokinetic analysis of 53 patients from a study in paediatric patients with SLE. Following intravenous administration of 10 mg/kg body weight 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 C_{max}, C_{min}, and AUC values were 305 µg/mL, 42 µg/mL, and 2569 day•µg/mL in the 5- to 11-year-old-group, and 317 µg/mL, 52 µg/mL, and 3126 day•µg/mL in the 12- to 17-year-old-group (n = 43).

Elderly: Benlysta 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, an effect of age cannot be ruled out conclusively.

Renal impairment: No specific studies have been conducted to examine the effects of renal impairment on the pharmacokinetics of belimumab. During clinical development Benlysta was studied in patients with SLE and renal impairment (261 subjects with moderate renal impairment, creatinine clearance ≥ 30 and < 60 mL/min; 14 subjects with severe renal impairment, creatinine clearance ≥ 15 and < 30 mL/min). The reduction in systemic clearance estimated by population pharmacokinetic modelling for patients at the midpoints of the renal impairment categories relative to patients with median creatinine clearance in the pharmacokinetic population (79.9 mL/min) were 1.4 % for mild (75 mL/min), 11.7 % for moderate (45 mL/min) and 24.0 % for severe (22.5 mL/min) renal impairment. 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.

Hepatic impairment: No specific studies have been 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 and changes in hepatic function are unlikely to have any effect on the elimination of belimumab.

Body weight/Body Mass Index (BMI)

Weight-normalised belimumab dosing leads to decreased exposure for underweight subjects (BMI < 18.5) and to increased exposure for obese subjects (BMI ≥ 30). BMI-dependent changes in exposure did not lead to corresponding changes in efficacy. Increased exposure for obese subjects receiving belimumab 10 mg/kg body weight did not lead to an overall increase in AE rates or serious AEs compared to obese subjects receiving placebo. However, higher rates of nausea, vomiting and diarrhoea were observed in obese patients. None of these gastrointestinal events in obese patients were serious. No dose adjustment is recommended for underweight or obese subjects.

Transitioning from intravenous to subcutaneous administration

SLE
Patients with SLE transitioning from 10 mg/kg body weight intravenously every 4 weeks to a 200 mg subcutaneous regimen 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). Based on simulations with population pharmacokinetic parameters, the steady-state average belimumab concentrations for 200 mg subcutaneous every week (in adult patients, and in paediatric patients 5 to under 18 years of age and ≥ 50 kg), every 10 days (in paediatric patients 5 to under 18 years of age and 30 to < 50 kg) or every 2 weeks (in paediatric patients 5 to under 18 years of age and 15 to < 30 kg), were similar to 10 mg/kg body weight intravenous every 4 weeks.

Lupus nephritis
One to 2 weeks after completing the first 2 intravenous doses, patients with lupus nephritis transitioning from 10 mg/kg body weight intravenously to 200 mg subcutaneously weekly, are predicted to have average belimumab serum concentrations similar to patients dosed with 10 mg/kg body weight intravenously every 4 weeks based on population pharmacokinetic simulations (see section 4.2).

5.3 Preclinical safety data

Non-clinical data reveal 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 the 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 body weight by intravenous infusion (approximately 9 times the anticipated maximum human clinical exposure) every 2 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 3 months of life in infant monkeys; IgM levels in infants exposed to belimumab *in utero* recovered by 6 months of age.

Effects on male and female fertility in monkeys were assessed in the 6-month repeat dose toxicology studies of belimumab at doses up to and including 50 mg/kg body weight. No treatment-related changes were noted in the male and female reproductive organs of sexually mature animals. An informal assessment of menstrual cycling in females demonstrated no belimumab-related changes.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid monohydrate (E 330)
Sodium citrate (E 331)
Sucrose
Polysorbate 80 (E 433)

6.2 Incompatibilities

Benlysta is not compatible with 5 % glucose.

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vials

5 years.

Reconstituted solution

After reconstitution with water for injection, the reconstituted solution, if not used immediately, must be protected from direct sunlight, and stored refrigerated at 2 °C to 8 °C.

Reconstituted and diluted solution for infusion

Solution of Benlysta diluted in sodium chloride 9 mg/mL (0.9 %), sodium chloride 4.5 mg/mL (0.45 %), or Lactated Ringer's solution for infusion may be stored at 2 °C to 8 °C or room temperature (15 °C to 25 °C).

The total time from reconstitution of Benlysta to completion of infusion must not exceed 8 hours.

6.4 Special precautions for storage

Store in a refrigerator (2 °C to 8 °C).
Do not freeze.
Store in the original carton in order to protect from light.

For storage conditions after reconstitution and dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Benlysta 120 mg powder for concentrate for solution for infusion

Type 1 glass vials (5 mL), sealed with a siliconised chlorobutyl rubber stopper and a flip-off aluminium seal containing 120 mg of powder.

Pack size: 1 vial

Benlysta 400 mg powder for concentrate for solution for infusion

Type 1 glass vials (20 mL), sealed with a siliconised chlorobutyl rubber stopper and a flip-off aluminium seal containing 400 mg of powder.

Pack size: 1 vial

6.6 Special precautions for disposal and other handling

Preparation of 120 mg solution for infusion

Reconstitution
Reconstitution and dilution must be carried out under aseptic conditions.

Allow 10 to 15 minutes for the vial to warm to room temperature (15 °C to 25 °C).

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 belimumab is reconstituted with 1.5 mL of water for injection to yield a final concentration of 80 mg/mL belimumab.

The stream of water for injection needs to 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 (15 °C to 25 °C) 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 water has been added, but it may take up to 30 minutes.

Protect the reconstituted solution from sunlight.

If a mechanical reconstitution device is used to reconstitute Benlysta it must not exceed 500 rpm and the vial is not to be swirled for 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.

After reconstitution, a volume of 1.5 mL (corresponding to 120 mg belimumab) can be withdrawn from each vial.

Dilution
The reconstituted medicinal product is diluted to 250 mL with sodium chloride 9 mg/mL (0.9 %), sodium chloride 4.5 mg/mL (0.45 %), or Lactated Ringer's solution for infusion. For patients whose body weight is less than or equal to 40 kg, infusion bags with 100 mL of these diluents may be considered providing that the resulting belimumab concentration in the infusion bag does not exceed 4 mg/mL.

5 % glucose intravenous solutions are incompatible with Benlysta and must not be used.

From a 250 mL (or 100 mL) infusion bag or bottle of sodium chloride 9 mg/mL (0.9 %), sodium chloride 4.5 mg/mL (0.45 %), or Lactated Ringer's solution for infusion, 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 total time from reconstitution of Benlysta to completion of infusion must not exceed 8 hours.

<u>Preparation of 400 mg solution for infusion</u>

Reconstitution
Reconstitution and dilution must be carried out under aseptic conditions.

Allow 10 to 15 minutes for the vial to warm to room temperature (15 °C to 25 °C).

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

The 400 mg single-use vial of belimumab is reconstituted with 4.8 mL of water for injection to yield a final concentration of 80 mg/mL belimumab.

The stream of water for injection needs to 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 (15 °C to 25 °C) 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 water has been added, but it may take up to 30 minutes.

Protect the reconstituted solution from sunlight.

If a mechanical reconstitution device is used to reconstitute Benlysta it must not exceed 500 rpm and the vial is not to be swirled for 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.

After reconstitution, a volume of 5 mL (corresponding to 400 mg belimumab) can be withdrawn from each vial.

Dilution
The reconstituted medicinal product is diluted to 250 mL with sodium chloride 9 mg/mL (0.9 %), sodium chloride 4.5 mg/mL (0.45 %), or Lactated Ringer's solution for infusion.

5 % glucose intravenous solutions are incompatible with Benlysta and must not be used.

From a 250 mL infusion bag or bottle of sodium chloride 9 mg/mL (0.9 %), sodium chloride 4.5 mg/mL (0.45 %), or Lactated Ringer's solution for infusion, 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 total time from reconstitution of Benlysta to completion of infusion must not exceed 8 hours.

Method of administration

Benlysta is infused over a 1 hour period.

Benlysta must not be infused concomitantly in the same intravenous line with other agents. No physical or biochemical compatibility studies have been conducted to evaluate the co-administration of Benlysta with other agents.

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

Disposal

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

7. MARKETING AUTHORISATION HOLDER

GlaxoSmithKline (Ireland) Limited
12 Riverwalk
Citywest Business Campus
Dublin 24
Ireland

8. MARKETING AUTHORISATION NUMBERS

EU/1/11/700/001 1 vial – 120 mg
EU/1/11/700/002 1 vial – 400 mg

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 13 July 2011
Date of latest renewal: 18 February 2016

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers of the biological active substance

Human Genome Sciences, Inc.
Belward Small Scale Manufacturing (SSM) Facility
9910 Belward Campus Drive
Rockville, MD 20850
USA

OR

Human Genome Sciences, Inc.
Belward Large Scale Manufacturing (LSM) Facility
9911 Belward Campus Drive
Rockville, MD 20850
USA

OR

Samsung Biologics Co. Ltd
300, Songdo bio-daero,
Yeonsu-gu, Incheon, 21987,
Korea, Republic of

Name and address of the manufacturer responsible for batch release

GlaxoSmithKline Manufacturing S.P.A
Strada Provinciale Asolana No. 90
I-43056 San Polo di Torrile, Parma
Italy

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2)

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2. of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Obligation to complete post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	**Due date**
The MAH shall also provide a data report on a long-term controlled safety registry where all patients are followed for a minimum of 5 years, based on a protocol agreed with CHMP. The safety registry will evaluate the incidence of all-cause mortality and adverse events of special interest in patients with systemic lupus erythematosus. These adverse events of special interest include serious infections (including opportunistic infections and PML), selected serious psychiatric events, and malignancies (including non-melanoma skin cancer).	28 February 2026

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON – PRE-FILLED PEN(S)

1. NAME OF THE MEDICINAL PRODUCT

Benlysta 200 mg solution for injection in pre-filled pen

belimumab

2. STATEMENT OF ACTIVE SUBSTANCE

Each 1 mL pre-filled pen contains 200 mg belimumab

3. LIST OF EXCIPIENTS

Also contains: arginine hydrochloride, histidine, histidine monohydrochloride, polysorbate 80 (E 433), sodium chloride, water for injection.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled pen.

1 pre-filled pen.
4 pre-filled pens.

5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use.
Subcutaneous use.
For single use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING, IF NECESSARY

PRESS HERE TO OPEN

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

GlaxoSmithKline (Ireland) Limited, 12 Riverwalk, Citywest Business Campus, Dublin 24, Ireland

12. MARKETING AUTHORISATION NUMBERS

EU/1/11/700/003 1 pre-filled pen
EU/1/11/700/004 4 pre-filled pens

13. BATCH NUMBER, DONATION AND PRODUCT CODES

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

benlysta pen

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON – Multipack containing 12 pre-filled pens **(3 packs of 4** pre-filled pens**)-with blue box**

1. NAME OF THE MEDICINAL PRODUCT

Benlysta 200 mg solution for injection in pre-filled pen

belimumab

2. STATEMENT OF ACTIVE SUBSTANCE

Each 1 mL pre-filled pen contains 200 mg belimumab.

3. LIST OF EXCIPIENTS

Also contains: arginine hydrochloride, histidine, histidine monohydrochloride, polysorbate 80 (E 433), sodium chloride, water for injection.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled pen.

Multipack:12 pre-filled pens (3 cartons of 4 pre-filled pens).
Do not sell separately.

5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use.
Subcutaneous use.
For single use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

GlaxoSmithKline (Ireland) Limited
12 Riverwalk
Citywest Business Campus
Dublin 24
Ireland

12. MARKETING AUTHORISATION NUMBER

EU/1/11/700/005

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

benlysta pen

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON INTERMEDIATE PACKAGING

CARTON –- PRE-FILLED PEN- Multipack containing 12 pre-filled pens **(3 packs of 4** pre-filled pens**)- with out blue box**

1. NAME OF THE MEDICINAL PRODUCT

Benlysta 200 mg solution for injection in pre-filled pen

belimumab

2. STATEMENT OF ACTIVE SUBSTANCE

Each 1 mL pre-filled pen contains 200 mg belimumab

3. LIST OF EXCIPIENTS

Also contains: arginine hydrochloride, histidine, histidine monohydrochloride, polysorbate 80 (E 433), sodium chloride, water for injection.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled pen.

4 pre-filled pens. Component of a multipack.
Do not sell separately.

5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use.
Subcutaneous use.
For single use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

GlaxoSmithKline (Ireland) Limited
12 Riverwalk
Citywest Business Campus
Dublin 24
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

benlysta pen

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
PRE-FILLED PEN LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Benlysta 200 mg injection

belimumab
SC
Subcutaneous

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 mL

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON - PRE-FILLED SYRINGE(S)

1. NAME OF THE MEDICINAL PRODUCT

Benlysta 200 mg solution for injection in pre-filled syringe

belimumab

2. STATEMENT OF ACTIVE SUBSTANCE

Each 1 mL pre-filled syringe contains 200 mg belimumab

3. LIST OF EXCIPIENTS

Also contains: arginine hydrochloride, histidine, histidine monohydrochloride, polysorbate 80 (E 433), sodium chloride, water for injection.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled syringe.

1 pre-filled syringe.
4 pre-filled syringes.

5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use.
Subcutaneous use.
For single use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING, IF NECESSARY

PRESS HERE TO OPEN

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

GlaxoSmithKline (Ireland) Limited, 12 Riverwalk, Citywest Business Campus, Dublin 24, Ireland

12. MARKETING AUTHORISATION NUMBERS

EU/1/11/700/006 1 pre-filled syringe
EU/1/11/700/007 4 pre-filled syringes

13. BATCH NUMBER, DONATION AND PRODUCT CODES

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

benlysta syringe

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED SYRINGE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Benlysta 200 mg

belimumab
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 mL

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON-VIAL

1. NAME OF THE MEDICINAL PRODUCT

Benlysta 120 mg powder for concentrate for solution for infusion

belimumab

2. STATEMENT OF ACTIVE SUBSTANCE

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

3. LIST OF EXCIPIENTS

Citric acid monohydrate (E 330), sodium citrate (E 331), sucrose, polysorbate 80 (E 433)

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for concentrate for solution for infusion
1 vial

5. METHOD AND ROUTE OF ADMINISTRATION

For intravenous infusion after reconstitution and dilution.
Read the package leaflet before use.
Intravenous use.
For single use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

GlaxoSmithKline (Ireland) Limited, 12 Riverwalk, Citywest Business Campus, Dublin 24, Ireland

12. MARKETING AUTHORISATION NUMBER

EU/1/11/700/001

13. BATCH NUMBER, DONATION AND PRODUCT CODES

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Benlysta 120 mg powder for concentrate for solution for infusion

belimumab
IV

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

120 mg

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON-VIAL

1. NAME OF THE MEDICINAL PRODUCT

Benlysta 400 mg powder for concentrate for solution for infusion

belimumab

2. STATEMENT OF ACTIVE SUBSTANCE

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

3. LIST OF EXCIPIENTS

Citric acid monohydrate (E 330), sodium citrate (E 331), sucrose, polysorbate 80 (E 433)

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for concentrate for solution for infusion
1 vial

5. METHOD AND ROUTE OF ADMINISTRATION

For intravenous infusion after reconstitution and dilution.
Read the package leaflet before use.
Intravenous use.
For single use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

GlaxoSmithKline (Ireland) Limited, 12 Riverwalk, Citywest Business Campus, Dublin 24, Ireland

12. MARKETING AUTHORISATION NUMBER

EU/1/11/700/002

13. BATCH NUMBER, DONATION AND PRODUCT CODES

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Benlysta 400 mg powder for concentrate for solution for infusion

belimumab
IV

2. METHOD AND ROUTE OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

400 mg

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Benlysta 200 mg solution for injection in pre-filled pen
belimumab

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Benlysta is and what it is used for

Benlysta as a subcutaneous injection is a medicine used to treat lupus (systemic lupus erythematosus, SLE) in adults (18 years of age and older) and children (5 to under 18 years of age and weighing at least 15 kg) whose disease is still highly active despite standard treatment. Benlysta is also used in combination with other medicines to treat adults (18 years of age and older) with active lupus nephritis (lupus-related kidney inflammation).

Lupus is a disease in which the immune system (the system that fights infection) attacks your own cells and tissues, causing inflammation and organ damage. It can affect almost any organ in the body, and is thought to involve a type of white blood cells called *B cells*.

Benlysta contains **belimumab** (*a monoclonal antibody*). It reduces the number of B cells in your blood by blocking the action of BLyS, a protein that helps B cells to live longer and is found in high levels in people with lupus.

You will be given Benlysta as well as your usual treatment for lupus.

2. What you need to know before you use Benlysta

Do not use Benlysta

- if you are **allergic** to belimumab or any of the other ingredients of this medicine (listed in section 6).
  ➔ **Check with your doctor** if this may apply to you.

Warnings and precautions
Talk to your doctor before you use Benlysta:

- if you have a current or long-term **infection** or if you often get infections. Your doctor will decide if you can be given Benlysta
- if you are planning to have a **vaccination** or have had a vaccination within the last 30 days. Some vaccines should not be given just before or during treatment with Benlysta
- if your lupus affects your **nervous system**
- if you are **HIV positive** or have **low immunoglobulin** levels
- if you have, or have had, **hepatitis B or C**
- if you have had an **organ transplant,** or a **bone marrow** or **stem cell transplant**
- if you have had **cancer**.
- if you have ever developed a **severe skin rash** or **skin peeling**, **blistering** and/or **mouth sores** after using Benlysta.

➔ **Tell your doctor** if any of these may apply to you.

Depression and suicide
There have been reports of depression, suicidal thoughts, and suicide attempts including suicide during treatment with Benlysta. Tell your doctor if you have a history of these conditions. If you experience new or worsening symptoms at any time:

➔ **Contact your doctor or go to a hospital straight away**.

If you feel depressed or have thoughts of harming yourself or committing suicide, you may find it helpful to tell a relative or close friend and ask them to read this leaflet. You might ask them to tell you if they are worried about changes in your mood or behaviour.

Severe skin reactions
Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported in association with Benlysta treatment.

➔ **Stop using Benlysta and seek medical attention immediately if you notice any of the symptoms described in section 4.**

Look out for important symptoms
People taking medicines that affect their immune system may be more at risk of infections, including a rare but serious brain infection called *progressive multifocal leukoencephalopathy* (PML).

➔ **Read the information 'Increased risk of brain infection' in section 4 of this leaflet.**

To improve the traceability of this medicine, you and your healthcare provider should record the Benlysta lot number. It is recommended that you make a note of this information in case you are asked for it in the future.

Children and adolescents
Benlysta pre-filled pen as a subcutaneous injection is not intended to be used in children younger than 5 years of age or less than 15 kg for the treatment of SLE.

Benlysta pre-filled pen as a subcutaneous injection is not intended to be used in children or adolescents younger than 18 years of age for the treatment of lupus nephritis.

Other medicines and Benlysta

Tell your doctor if you are taking any other medicines, if you have recently taken or might take any other medicines.

In particular tell your doctor if you are being treated with medicines that affect your immune system, including any medicine that affects your B cells (to treat cancer or inflammatory diseases).

Using such medicines in combination with Benlysta may make your immune system less effective. This could increase your risk of a serious infection.

Pregnancy and breast-feeding

Contraception for women who could become pregnant

- **Use an effective method of contraception** while you are being treated with Benlysta and for at least 4 months after the last dose.

Pregnancy

Benlysta is not usually recommended if you are pregnant.

- **Tell your doctor if you are pregnant,** think you may be pregnant, or are planning to have a baby. Your doctor will decide if you can use Benlysta.
- **If you become pregnant** while being treated with Benlysta, tell your doctor.

Breast-feeding

Tell your doctor if you are breast-feeding. It is likely that Benlysta can pass into breast milk. Your doctor will discuss with you whether you should stop treatment with Benlysta while you are breast-feeding, or if you should stop breast-feeding.

Driving and using machines
Benlysta can have side effects which may make you less able to drive or use machines.

Benlysta contains polysorbate 80
This medicine contains 0.1 mg of polysorbate 80 in each pre-filled pen. Polysorbates may cause allergic reactions. Tell your doctor if you have or your child has any known allergies.

Benlysta contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per dose, so it is essentially 'sodium-free'.

3. How Benlysta is used

Always use this medicine exactly as your doctor or pharmacist has told you to. Check with your doctor or pharmacist if you are not sure.

Benlysta must be injected under your skin following the schedule prescribed to you by your doctor.

How much to use

Systemic lupus erythematosus

Adults
The recommended dose is 200 mg (complete contents of one pen) once a week.

Children and adolescents 5 years and older
The recommended dose for children and adolescents 5 years and older is based on weight as shown below:

Body weight	Recommended dose
50 kg or more	200 mg (complete contents of one pen) once a week
30 kg to less than 50 kg	200 mg (complete contents of one pen) once every 10 days
15 kg to less than 30 kg	200 mg (complete contents of one pen) once every 2 weeks

Lupus nephritis

Adults only
The recommended dose may vary. Your doctor will prescribe the right dose for you, which is either:

- a dose of 200 mg (complete contents of one pen) once a week.
  or
- a dose of 400 mg (complete contents of two pens in one day) once a week for 4 weeks. After this, the recommended dose is 200 mg (complete contents of one pen) once a week.

If you wish to change your dosing day
Take a dose on the new day (even if the time since your last dose is less than usual). Continue with the new schedule from that day.

Injecting Benlysta
Your doctor or nurse will show you or your caregiver how to inject Benlysta. Your first injection with the Benlysta pre-filled pen will be supervised by your doctor or nurse. After you have been trained on how to use the pen, your doctor or nurse may decide that you can give yourself the injection, or your caregiver can give it to you. Your doctor or nurse will also tell you what signs and symptoms to look out for when using Benlysta, because serious allergic reactions can occur (see *'Allergic reactions'* in section 4).

For children under 10 years of age, the Benlysta pre-filled pen must be injected by a doctor, nurse, or trained caregiver.

You inject Benlysta under your skin in your stomach area (abdomen) or upper leg (thigh).

Benlysta subcutaneous injection must not be injected into a vein (*intravenously*).

Instructions for using the pre-filled pen are given at the end of this leaflet.

If you use more Benlysta than you should
If this happens, immediately contact your doctor or nurse, who will monitor you for any signs or symptoms of side effects, and treat these symptoms if necessary. If possible show them the pack, or this leaflet.

If you forget to use Benlysta
Inject the missed dose as soon as you remember. Then continue with your normal weekly schedule as usual or start a new weekly schedule starting from the day you inject the missed dose.
If you do not notice that you have missed a dose until it is already time for your next dose, then just inject this next dose as planned.

Stopping treatment with Benlysta
Your doctor will decide if you need to stop using Benlysta.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Stop using Benlysta and seek medical attention immediately if you notice any of the following symptoms of a severe skin reaction:

- reddish patches on the trunk, the patches are target-like macules or circular, often with central blisters, skin peeling, ulcers of mouth, throat, nose, genitals and eyes. These severe skin rashes can be preceded by fever and flu-like symptoms (Stevens-Johnson syndrome and toxic epidermal necrolysis). These side effects have been reported with unknown frequency (cannot be estimated from the available data).

Allergic reactions — get medical help immediately
Benlysta can cause a reaction to the injection, or an allergic *(hypersensitivity)* reaction.
These are common side effects (may affect up to 1 in 10 people). They can occasionally be severe (uncommon, affecting up to 1 in 100 people), and could be life-threatening. These severe reactions are more likely to happen on the day of your first or second treatment with Benlysta, but can be delayed and occur several days afterwards.

Tell your doctor or nurse immediately, or go to the Emergency department of your nearest hospital, if you get any of the following symptoms of an allergic or injection-related reaction:
- swelling of the face, lips, mouth or tongue
- wheezing, difficulty in breathing or shortness of breath
- rash
- itchy raised bumps or hives.

Rarely, less severe delayed reactions to Benlysta can also occur, usually 5 to 10 days after an injection. They include symptoms such as rash, feeling sick, tiredness, muscle aches, headache, or facial swelling.
If you experience these symptoms, particularly if you get two or more of them together:
➔ **Tell your doctor or nurse.**

Infections
Benlysta can make you more likely to get infections, including infection of the urinary tract and airways. These are very common and may affect more than 1 in 10 people. Some infections can be severe and can uncommonly cause death.

If you get any of the following symptoms of an infection:
- fever and/or chills
- cough, breathing problems
- diarrhoea, vomiting
- burning sensation while passing urine; urinating often
- warm, red or painful skin or sores on your body.

➔ **Tell your doctor or nurse immediately.**

Depression and suicide
There have been reports of depression, suicidal thoughts, and suicide attempts during treatment with Benlysta. Depression can affect up to 1 in 10 people, suicidal thoughts and suicide attempts can affect up to 1 in 100 people. If you feel depressed, have thoughts about harming yourself or other distressing thoughts, or if you are depressed and notice that you feel worse or develop new symptoms:
➔ **Contact your doctor or go to a hospital straight away.**

Increased risk of brain infection
Medicines that weaken your immune system, such as Benlysta, may put you at higher risk of getting a rare but serious and life-threatening brain infection called *progressive multifocal leukoencephalopathy* (PML).

Symptoms of PML include:
- memory loss
- trouble in thinking
- difficulty with talking or walking
- loss of vision.

➔ **Tell your doctor immediately** if you have any of these symptoms, or similar problems that have lasted over several days.

If you already had these symptoms before you started treatment with Benlysta:
➔ **Tell your doctor immediately** if you notice any changes in these symptoms.

Other possible side effects:

Very common side effects
These may affect **more than 1 in 10** people:
- bacterial infections *(see 'Infections' above)*.

Common side effects
These may affect **up to 1 in 10** people:
- high temperature or fever
- injection site reactions, for example: rash, redness, itching or swelling of the skin where you have injected Benlysta
- itchy, bumpy rash (hives), skin rash
- low white blood cell count (can be seen in blood tests)
- nose, throat or stomach infection
- pain in hands or feet
- migraine
- feeling sick, diarrhoea.

Reporting of side effects
If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Benlysta

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label and carton after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2 °C to 8 °C).

Do not freeze.

Store in the original package in order to protect from light.

A single Benlysta pre-filled pen can be stored at room temperature (up to 25 °C) for a maximum of 12 hours – as long as it is protected from light. Once removed from the refrigerator, the pen **must be used within 12 hours or discarded**.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Benlysta contains
The active ingredient is belimumab.

Each 1 mL pre-filled pen contains 200 mg belimumab.

The other ingredients are arginine hydrochloride, histidine, histidine monohydrochloride, polysorbate 80 (E 433), sodium chloride, water for injection. See section 2 for further information on polysorbate 80 and sodium content.

What Benlysta looks like and contents of the pack
Benlysta is supplied as a 1 mL colourless to slightly yellow solution in a single use pre-filled pen.

Available in packs of 1 or 4 pre-filled pens in each pack and multipacks comprising 12 pre-filled pens (3 packs of 4 pre-filled pens).

Not all pack sizes may be marketed.

Marketing Authorisation Holder
GlaxoSmithKline (Ireland) Limited
12 Riverwalk
Citywest Business Campus
Dublin 24
Ireland

Manufacturer
GlaxoSmithKline Manufacturing S.P.A
Strada Provinciale Asolana, 90
43056 San Polo di Torrile
Parma
Italy

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
GlaxoSmithKline Pharmaceuticals s.a./n.v.
Tél/Tel: + 32 (0)10 85 52 00

Lietuva
GlaxoSmithKline Trading Services Limited
Tel: + 370 80000334

България
GlaxoSmithKline Trading Services Limited
Тел.: + 359 80018205

Luxembourg/Luxemburg
GlaxoSmithKline Pharmaceuticals s.a./n.v.
Belgique/Belgien
Tél/Tel: + 32 (0) 10 85 52 00

Česká republika
GlaxoSmithKline s.r.o.
Tel: + 420 222 001 111
cz.info@gsk.com

Magyarország
GlaxoSmithKline Trading Services Limited
Tel.: + 36 80088309

Danmark
GlaxoSmithKline Pharma A/S
Tlf.: + 45 36 35 91 00
dk-info@gsk.com

Malta
GlaxoSmithKline Trading Services Limited
Tel: + 356 80065004

Deutschland
GlaxoSmithKline GmbH & Co. KG
Tel.: + 49 (0)89 36044 8701
produkt.info@gsk.com

Nederland
GlaxoSmithKline BV
Tel: + 31 (0)33 2081100

Eesti
GlaxoSmithKline Trading Services Limited
Tel: + 372 8002640

Ελλάδα
GlaxoSmithKline Μονοπρόσωπη A.E.B.E.
Τηλ: + 30 210 68 82 100

España
GlaxoSmithKline, S.A.
Tel: + 34 900 202 700
es-ci@gsk.com

France
Laboratoire GlaxoSmithKline
Tél.: + 33 (0)1 39 17 84 44
diam@gsk.com

Hrvatska
GlaxoSmithKline Trading Services Limited
Tel:+ 385 800787089

Ireland
GlaxoSmithKline (Ireland) Limited
Tel: + 353 (0)1 4955000

Ísland
Vistor ehf.
Sími: +354 535 7000

Italia
GlaxoSmithKline S.p.A.
Tel: + 39 (0)45 7741111

Κύπρος
GlaxoSmithKline Trading Services Limited
Τηλ: + 357 80070017

Latvija
GlaxoSmithKline Trading Services Limited
Tel: + 371 80205045

Norge
GlaxoSmithKline AS
Tlf: + 47 22 70 20 00

Österreich
GlaxoSmithKline Pharma GmbH
Tel: + 43 (0)1 97075 0
at.info@gsk.com

Polska
GSK Services Sp. z o.o.
Tel.: + 48 (0)22 576 9000

Portugal
GlaxoSmithKline – Produtos Farmacêuticos, Lda.
Tel: + 351 21 412 95 00
FI.PT@gsk.com

România
GlaxoSmithKline Trading Services Limited
Tel: + 40 800672524

Slovenija
GlaxoSmithKline Trading Services Limited
Tel: + 386 80688869

Slovenská republika
GlaxoSmithKline Trading Services Limited
Tel: + 421 800500589

Suomi/Finland
GlaxoSmithKline Oy
Puh/Tel: + 358 (0)10 30 30 30

Sverige
GlaxoSmithKline AB
Tel: + 46 (0)8 638 93 00
info.produkt@gsk.com

This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.

Step-by-step instructions for using the pre-filled pen

Once weekly: for adults, and for children 5 to under 18 years of age and weighing 50 kg or more.

Once every 10 days: for children 5 to under 18 years of age and weighing 30 kg to less than 50 kg.

Once every 2 weeks: for children 5 to under 18 years of age and weighing 15 kg to less than 30 kg.

Read these sections first

Follow these instructions on how to use the pre-filled pen correctly. Failure to follow these instructions may affect proper function of the pre-filled pen. You will also need to receive training on how to use the pre-filled pen.

Benlysta is for use **under the skin only** (*subcutaneous*).

To improve the traceability of this medicine, you and your healthcare provider should record the Benlysta lot number. It is recommended that you make a note of this information in case you are asked for it in the future.

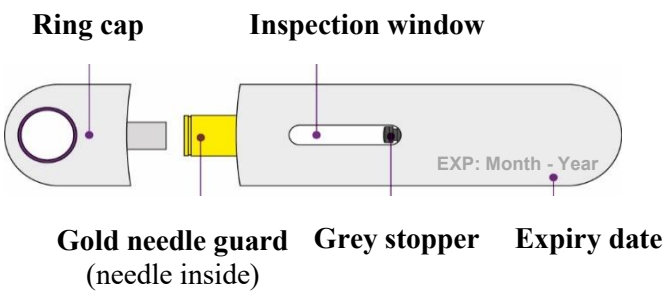
Storage

- Keep refrigerated until 30 minutes before use.
- Keep in the carton in order to protect from light.
- Keep out of the sight and reach of children.
- Keep away from heat and sunlight.
- **Do not** freeze. If the pen has been frozen, **do not** use the pen even if it is thawed.
- **Do not** use and **do not** place back in the refrigerator if left out at room temperature for more than 12 hours.

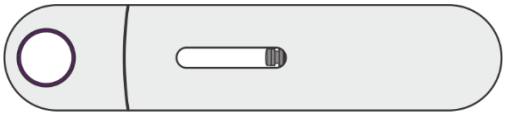
Warnings

- The pre-filled pen must only be used once and then discarded.
- **Do not** share your Benlysta pre-filled pen with another person.
- **Do not** shake.
- **Do not** use if dropped onto a hard surface.
- **Do not** remove the ring cap until just before the injection.

Benlysta pre-filled pen parts

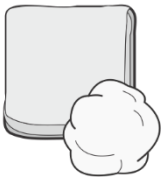


Supplies you need for the injection



Benlysta pre-filled pen

Alcohol swab
(not included)



Gauze pad or cotton wool ball
(not included)

1. Gather and check supplies

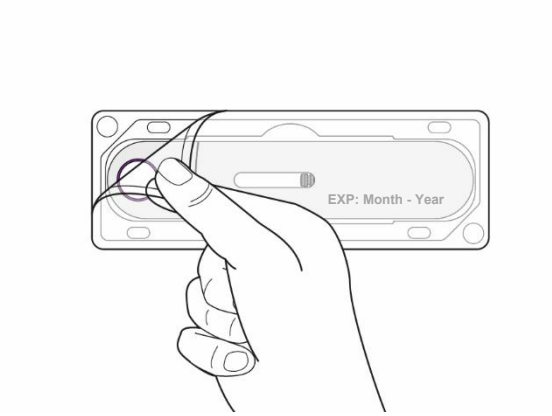
Gather supplies

- Remove one sealed tray containing a pre-filled pen from the refrigerator.
- Place any remaining pre-filled pens back into the refrigerator.
- Find a comfortable, well-lit and clean surface and place the following supplies within reach:
  - Benlysta pre-filled pen
  - alcohol swab (*not included in the pack*)
  - gauze pad or cotton wool ball (*not included in the pack*)
  - container with a tight-fitting lid for pen disposal (*not included in the pack*).
- **Do not** perform the injection if you do not have all the supplies listed.

Take out the pre-filled pen

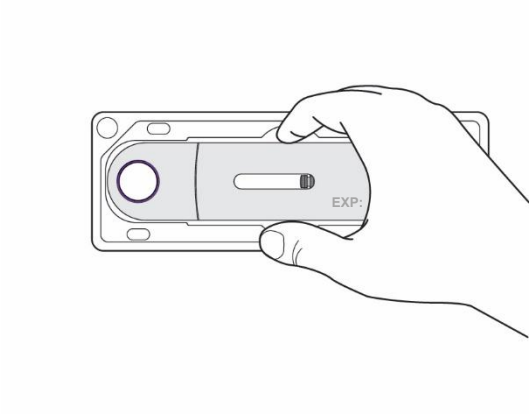
- Peel back the film from the corner of the tray. (*Figure 1*)

Figure 1



- Holding the middle of the pre-filled pen (near the inspection window), carefully take the pre-filled pen out of the tray. (*Figure 2*)

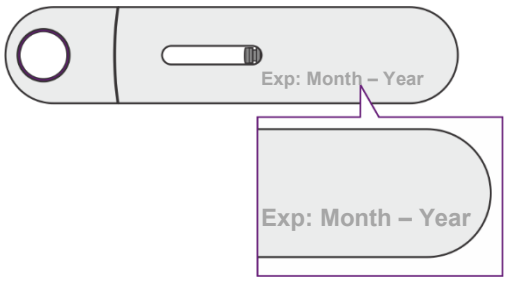
Figure 2



Check the expiry date

- Check the expiry date on the pre-filled pen. (*Figure 3*)

Figure 3



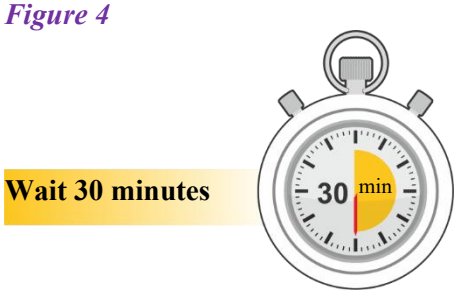
- **Do not** use if the expiry date has passed.

2. Prepare and inspect the pre-filled pen

Allow to come to room temperature

- Leave the pen at room temperature for 30 minutes. (*Figure 4*) Injecting cold Benlysta may take longer and may be uncomfortable.

Figure 4



- **Do not** warm the pen in any other way. For example, do not warm it in a microwave oven, hot water or direct sunlight.

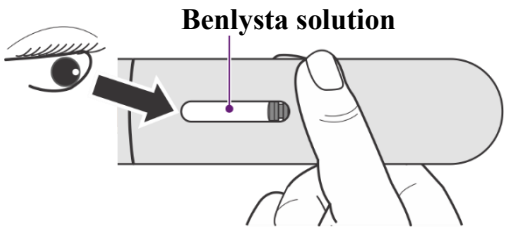
- **Do not** remove the ring cap during this step.

Inspect the Benlysta solution

- Look in the inspection window to check that the Benlysta solution is colourless to slightly yellow in colour. (*Figure 5*)

    - It is normal to see one or more air bubbles in the solution.

Figure 5



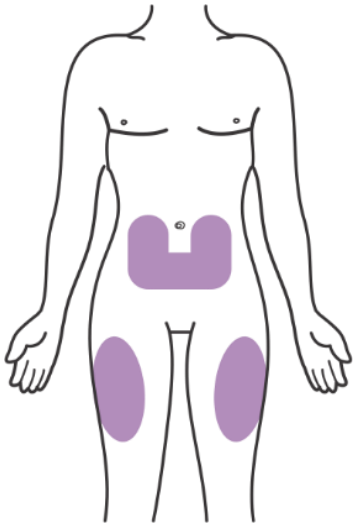
- **Do not** use if the solution looks cloudy, discoloured or has particles.

3. Choose and clean the injection site

Choose the injection site

- Choose an injection site (abdomen or thigh) as seen in *Figure 6*.

Figure 6

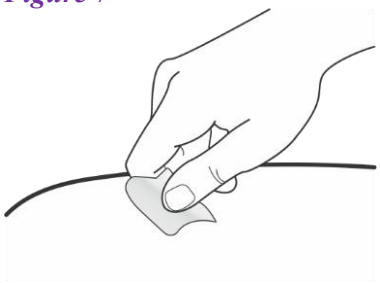


- If you need 2 injections to complete your dose, leave at least 5 cm (2 inches) between each injection if using the same site.
- **Do not** inject into the exact same site each time. This is to avoid the skin becoming hardened.
- **Do not** inject in areas where the skin is tender, bruised, red or hard.
- **Do not** inject within 5 cm (2 inches) of the navel (belly button).

Clean the injection site

- Wash your hands.
- Clean the injection site by wiping it with an alcohol swab (*Figure 7*). Allow the skin to air dry.

Figure 7



- **Do not** touch this area again before giving the injection.

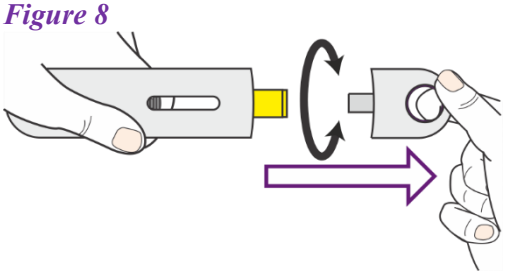
4. Prepare for the injection

Remove the ring cap

- **Do not** remove the ring cap until immediately before the injection.

- Remove the ring cap by pulling or twisting it off. The ring cap may be twisted off either clockwise or anti-clockwise. (*Figure 8*)

Figure 8

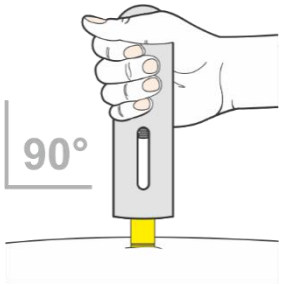


- **Do not** put the ring cap back onto the pen.

Position the pen

- Hold the pen comfortably so that you can view the inspection window. This is important so that you can confirm a complete dose. (*Figure 9*)

Figure 9



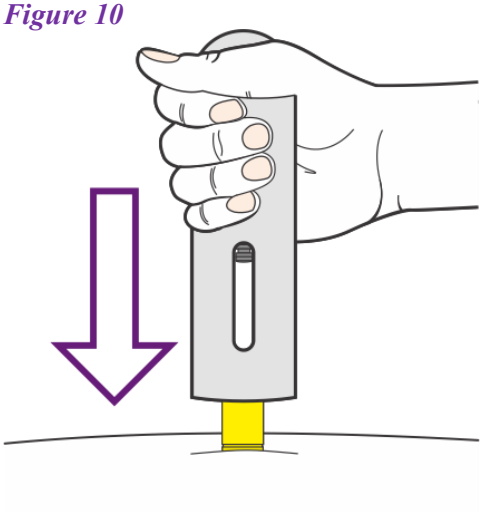
- If needed, firm the injection site by pulling or stretching the skin.
- Position the pen straight over the injection site (at a 90º angle). Make sure the gold needle guard is flat on the skin.

5. Inject Benlysta and inspect

Start the injection

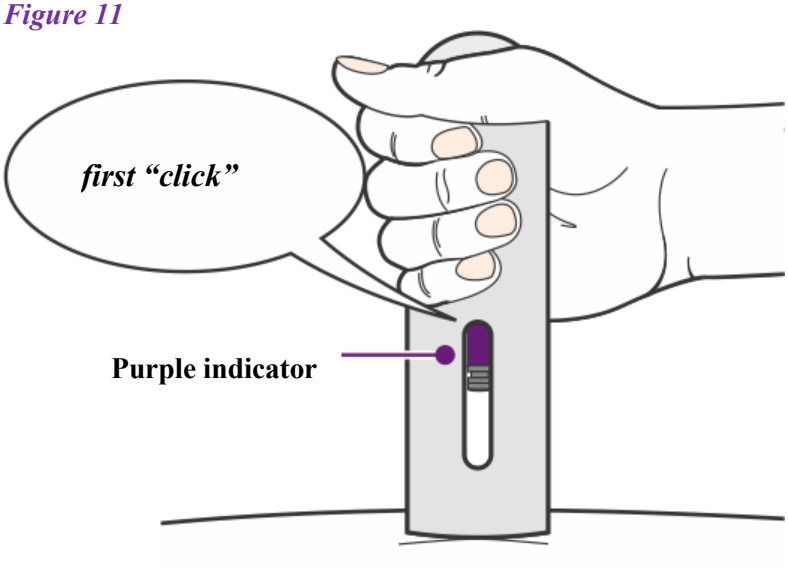
- Firmly press the pen all the way down onto the injection site and hold in place. (*Figure 10*)
    - This will insert the needle and start the injection.

Figure 10



- You may hear a first “click” at the start of the injection. You will see the purple indicator start to move through the inspection window. (*Figure 11*)

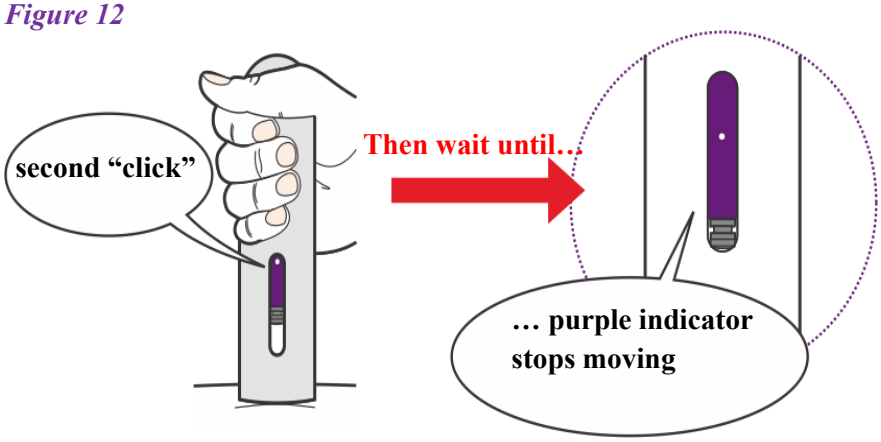
Figure 11



Complete the injection

- Continue to hold the pen down until the purple indicator has stopped moving.
    - You may hear a second “click” a few seconds before the purple indicator stops moving. (*Figure 12*)

Figure 12



    - The injection may take up to 15 seconds to complete.
- When the injection is complete, lift the pen from the injection site.

Inspect the injection site

There may be a small amount of blood at the injection site.

- If needed, press a cotton ball or gauze pad on the injection site.
- **Do not** rub the injection site.

6. Dispose of used pen

Dispose of the used pen

- **Do not** put the ring cap back onto the pen.
- Dispose of the used pen and ring cap in a container with a tight-fitting lid.
- Ask your doctor or pharmacist for instructions on how to properly dispose of a used pen or container of used pens.
- **Do not** recycle or throw the used pen, or the container of used pens, in household waste.

Package leaflet: Information for the user

Benlysta 200 mg solution for injection in pre-filled syringe
belimumab

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Benlysta is and what it is used for

Benlysta as a subcutaneous injection is a medicine used to treat lupus (systemic lupus erythematosus, SLE) in adults (18 years of age and older) whose disease is still highly active despite standard treatment. Benlysta is also used in combination with other medicines to treat adults (18 years of age and older) with active lupus nephritis (lupus-related kidney inflammation).

Lupus is a disease in which the immune system (the system that fights infection) attacks your own cells and tissues, causing inflammation and organ damage. It can affect almost any organ in the body, and is thought to involve a type of white blood cells called *B cells*.

Benlysta contains **belimumab** (*a monoclonal antibody*). It reduces the number of B cells in your blood by blocking the action of BLyS, a protein that helps B cells to live longer and is found in high levels in people with lupus.

You will be given Benlysta as well as your usual treatment for lupus.

2. What you need to know before you use Benlysta

Do not use Benlysta

- if you are **allergic** to belimumab or any of the other ingredients of this medicine (listed in section 6).
  ➔ **Check with your doctor** if this may apply to you.

Warnings and precautions
Talk to your doctor before you use Benlysta:

- if you have a current or long-term **infection** or if you often get infections. Your doctor will decide if you can be given Benlysta
- if you are planning to have a **vaccination** or have had a vaccination within the last 30 days. Some vaccines should not be given just before or during treatment with Benlysta
- if your lupus affects your **nervous system**
- if you are **HIV positive** or have **low immunoglobulin** levels
- if you have, or have had, **hepatitis B or C**
- if you have had an **organ transplant,** or a **bone marrow** or **stem cell transplant**
- if you have had **cancer**.
- if you have ever developed a **severe skin rash** or **skin peeling**, **blistering** and/or **mouth sores** after using Benlysta.

➔ **Tell your doctor** if any of these may apply to you.

Depression and suicide
There have been reports of depression, suicidal thoughts, and suicide attempts including suicide during treatment with Benlysta. Tell your doctor if you have a history of these conditions. If you experience new or worsening symptoms at any time:

➔ **Contact your doctor or go to a hospital straight away**.

If you feel depressed or have thoughts of harming yourself or committing suicide, you may find it helpful to tell a relative or close friend and ask them to read this leaflet. You might ask them to tell you if they are worried about changes in your mood or behaviour.

Severe skin reactions
Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported in association with Benlysta treatment.

➔ **Stop using Benlysta and seek medical attention immediately if you notice any of the symptoms described in section 4.**

Look out for important symptoms
People taking medicines that affect their immune system may be more at risk of infections, including a rare but serious brain infection called *progressive multifocal leukoencephalopathy* (PML).

➔ **Read the information 'Increased risk of brain infection' in section 4 of this leaflet.**

To improve the traceability of this medicine, you and your healthcare provider should record the Benlysta lot number. It is recommended that you make a note of this information in case you are asked for it in the future.

Children and adolescents
Benlysta pre-filled syringe as a subcutaneous injection is not intended to be used in children or adolescents younger than 18 years of age.

Other medicines and Benlysta

Tell your doctor if you are taking any other medicines, if you have recently taken or might take any other medicines.

In particular tell your doctor if you are being treated with medicines that affect your immune system, including any medicine that affects your B cells (to treat cancer or inflammatory diseases).

Using such medicines in combination with Benlysta may make your immune system less effective. This could increase your risk of a serious infection.

Pregnancy and breast-feeding

Contraception for women who could become pregnant

- **Use an effective method of contraception** while you are being treated with Benlysta and for at least 4 months after the last dose.

Pregnancy

Benlysta is not usually recommended if you are pregnant.

- **Tell your doctor if you are pregnant,** think you may be pregnant, or are planning to have a baby. Your doctor will decide if you can use Benlysta.
- **If you become pregnant** while being treated with Benlysta, tell your doctor.

Breast-feeding

Tell your doctor if you are breast-feeding. It is likely that Benlysta can pass into breast milk. Your doctor will discuss with you whether you should stop treatment with Benlysta while you are breast-feeding, or if you should stop breast-feeding.

Driving and using machines
Benlysta can have side effects which may make you less able to drive or use machines.

Benlysta contains polysorbate 80
This medicine contains 0.1 mg of polysorbate 80 in each pre-filled syringe. Polysorbates may cause allergic reactions. Tell your doctor if you have any known allergies.

Benlysta contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per dose, so it is essentially 'sodium-free'.

3. How Benlysta is used

Always use this medicine exactly as your doctor or pharmacist has told you to. Check with your doctor or pharmacist if you are not sure.

Benlysta must be injected under your skin on the same day each week.

How much to use

Adults (18 years of age and older)

Systemic lupus erythematosus
The recommended dose is 200 mg (complete contents of one syringe) once a week.

Lupus nephritis
The recommended dose may vary. Your doctor will prescribe the right dose for you, which is either:

- a dose of 200 mg (complete contents of one syringe) once a week.
  or
- a dose of 400 mg (complete contents of two syringes in one day) once a week for 4 weeks. After this, the recommended dose is 200 mg (complete contents of one syringe) once a week.

If you wish to change your dosing day
Take a dose on the new day (even if it is less than a week since your last dose). Continue with the new weekly schedule from that day.

Injecting Benlysta
Your doctor or nurse will show you or your caregiver how to inject Benlysta. Your first injection with the Benlysta pre-filled syringe will be supervised by your doctor or nurse. After you have been trained on how to use the syringe, your doctor or nurse may decide that you can give yourself the injection, or your caregiver can give it to you. Your doctor or nurse will also tell you what signs and symptoms to look out for when using Benlysta, because serious allergic reactions can occur (see *'Allergic reactions'* in section 4).

You inject Benlysta under your skin in your stomach area (abdomen) or upper leg (thigh).

Benlysta subcutaneous injection must not be injected into a vein (*intravenously*).

Instructions for using the pre-filled syringe are given at the end of this leaflet.

If you use more Benlysta than you should
If this happens, immediately contact your doctor or nurse, who will monitor you for any signs or symptoms of side effects, and treat these symptoms if necessary. If possible show them the pack, or this leaflet.

If you forget to use Benlysta
Inject the missed dose as soon as you remember. Then continue with your normal weekly schedule as usual or start a new weekly schedule starting from the day you inject the missed dose.
If you do not notice that you have missed a dose until it is already time for your next dose, then just inject this next dose as planned.

Stopping treatment with Benlysta
Your doctor will decide if you need to stop using Benlysta.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Stop using Benlysta and seek medical attention immediately if you notice any of the following symptoms of a severe skin reaction:
- reddish patches on the trunk, the patches are target-like macules or circular, often with central blisters, skin peeling, ulcers of mouth, throat, nose, genitals and eyes. These severe skin rashes can be preceded by fever and flu-like symptoms (Stevens-Johnson syndrome and toxic epidermal necrolysis). These side effects have been reported with unknown frequency (cannot be estimated from the available data).

Allergic reactions — get medical help immediately
Benlysta can cause a reaction to the injection, or an allergic *(hypersensitivity)* reaction.
These are common side effects (may affect up to 1 in 10 people). They can occasionally be severe (uncommon, affecting up to 1 in 100 people), and could be life-threatening. These severe reactions are more likely to happen on the day of your first or second treatment with Benlysta, but can be delayed and occur several days afterwards.

Tell your doctor or nurse immediately, or go to the Emergency department of your nearest hospital, if you get any of the following symptoms of an allergic or injection-related reaction:
- swelling of the face, lips, mouth or tongue
- wheezing, difficulty in breathing or shortness of breath
- rash
- itchy raised bumps or hives.

Rarely, less severe delayed reactions to Benlysta can also occur, usually 5 to 10 days after an injection. They include symptoms such as rash, feeling sick, tiredness, muscle aches, headache, or facial swelling.
If you experience these symptoms, particularly if you get two or more of them together:
➔ **Tell your doctor or nurse.**

Infections
Benlysta can make you more likely to get infections, including infection of the urinary tract and airways. These are very common and may affect more than 1 in 10 people. Some infections can be severe and can uncommonly cause death.

If you get any of the following symptoms of an infection:
- fever and/or chills
- cough, breathing problems
- diarrhoea, vomiting
- burning sensation while passing urine; urinating often
- warm, red or painful skin or sores on your body.

➔ **Tell your doctor or nurse immediately.**

Depression and suicide
There have been reports of depression, suicidal thoughts, and suicide attempts during treatment with Benlysta. Depression can affect up to 1 in 10 people, suicidal thoughts and suicide attempts can affect up to 1 in 100 people. If you feel depressed, have thoughts about harming yourself or other distressing thoughts, or if you are depressed and notice that you feel worse or develop new symptoms:

➔ **Contact your doctor or go to a hospital straight away.**

Increased risk of brain infection
Medicines that weaken your immune system, such as Benlysta, can put you at higher risk of getting a rare but serious and life-threatening brain infection called *progressive multifocal leukoencephalopathy* (PML).

Symptoms of PML include:
- memory loss
- trouble in thinking
- difficulty with talking or walking
- loss of vision.

➔ **Tell your doctor immediately** if you have any of these symptoms, or similar problems that have lasted over several days.

If you already had these symptoms before you started treatment with Benlysta:

➔ **Tell your doctor immediately** if you notice any changes in these symptoms.

Other possible side effects:

Very common side effects
These may affect **more than 1 in 10** people:
- bacterial infections *(see 'Infections' above)*.

Common side effects
These may affect **up to 1 in 10** people:
- high temperature or fever
- injection site reactions, for example: rash, redness, itching or swelling of the skin where you have injected Benlysta
- itchy, bumpy rash (hives), skin rash
- low white blood cell count (can be seen in blood tests)
- nose, throat or stomach infection
- pain in hands or feet
- migraine
- feeling sick, diarrhoea.

Reporting of side effects
If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Benlysta

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label and carton after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2 °C to 8 °C).

Do not freeze.

Store in the original package in order to protect from light.

A single Benlysta pre-filled syringe can be stored at room temperature (up to 25 °C) for a maximum of 12 hours – as long as it is protected from light. Once removed from the refrigerator, the syringe **must be used within 12 hours or discarded**.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Benlysta contains
The active ingredient is belimumab.

Each 1 mL pre-filled syringe contains 200 mg belimumab.

The other ingredients are arginine hydrochloride, histidine, histidine monohydrochloride, polysorbate 80 (E 433), sodium chloride, water for injection. See section 2 for further information on polysorbate 80 and sodium content.

What Benlysta looks like and contents of the pack
Benlysta is supplied as a 1 mL colourless to slightly yellow solution in a single use pre-filled syringe with a needle cap.

Available in packs of 1 or 4 pre-filled syringes in each pack.

Not all pack sizes may be marketed.

Marketing Authorisation Holder
GlaxoSmithKline (Ireland) Limited
12 Riverwalk
Citywest Business Campus
Dublin 24
Ireland

Manufacturer
GlaxoSmithKline Manufacturing S.P.A
Strada Provinciale Asolana, 90
43056 San Polo di Torrile
Parma
Italy

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
GlaxoSmithKline Pharmaceuticals s.a./n.v.
Tél/Tel: + 32 (0)10 85 52 00

България
GlaxoSmithKline Trading Services Limited
Тел.: + 359 80018205

Česká republika
GlaxoSmithKline s.r.o.
Tel: + 420 222 001 111
cz.info@gsk.com

Danmark
GlaxoSmithKline Pharma A/S
Tlf.: + 45 36 35 91 00
dk-info@gsk.com

Deutschland
GlaxoSmithKline GmbH & Co. KG
Tel.: + 49 (0)89 36044 8701
produkt.info@gsk.com

Eesti
GlaxoSmithKline Trading Services Limited
Tel: + 372 8002640

Ελλάδα
GlaxoSmithKline Μονοπρόσωπη A.E.B.E.
Τηλ: + 30 210 68 82 100

España
GlaxoSmithKline, S.A.
Tel: + 34 900 202 700
es-ci@gsk.com

France
Laboratoire GlaxoSmithKline
Tél.: + 33 (0)1 39 17 84 44
diam@gsk.com

Hrvatska
GlaxoSmithKline Trading Services Limited
Tel:+ 385 800787089

Lietuva
GlaxoSmithKline Trading Services Limited
Tel: + 370 80000334

Luxembourg/Luxemburg
GlaxoSmithKline Pharmaceuticals s.a./n.v.
Belgique/Belgien
Tél/Tel: + 32 (0) 10 85 52 00

Magyarország
GlaxoSmithKline Trading Services Limited
Tel.: + 36 80088309

Malta
GlaxoSmithKline Trading Services Limited
Tel: + 356 80065004

Nederland
GlaxoSmithKline BV
Tel: + 31 (0)33 2081100

Norge
GlaxoSmithKline AS
Tlf: + 47 22 70 20 00

Österreich
GlaxoSmithKline Pharma GmbH
Tel: + 43 (0)1 97075 0
at.info@gsk.com

Polska
GSK Services Sp. z o.o.
Tel.: + 48 (0)22 576 9000

Portugal
GlaxoSmithKline – Produtos Farmacêuticos, Lda.
Tel: + 351 21 412 95 00
FI.PT@gsk.com

România
GlaxoSmithKline Trading Services Limited
Tel: + 40 800672524

Ireland
GlaxoSmithKline (Ireland) Limited
Tel: + 353 (0)1 4955000

Ísland
Vistor ehf.
Sími: +354 535 7000

Italia
GlaxoSmithKline S.p.A.
Tel: + 39 (0)45 7741111

Κύπρος
GlaxoSmithKline Trading Services Limited
Τηλ: + 357 80070017

Latvija
GlaxoSmithKline Trading Services Limited
Tel: + 371 80205045

Slovenija
GlaxoSmithKline Trading Services Limited
Tel: + 386 80688869

Slovenská republika
GlaxoSmithKline Trading Services Limited
Tel: + 421 800500589

Suomi/Finland
GlaxoSmithKline Oy
Puh/Tel: + 358 (0)10 30 30 30

Sverige
GlaxoSmithKline AB
Tel: + 46 (0)8 638 93 00
info.produkt@gsk.com

This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.

Step-by-step instructions for using the pre-filled syringe

Once weekly: for adults only

Read these sections first

Follow these instructions on how to use the pre-filled syringe correctly. Failure to follow these instructions may affect proper function of the pre-filled syringe. You will also need to receive training on how to use the pre-filled syringe.

Benlysta is for use **under the skin only** (*subcutaneous*).

To improve the traceability of this medicine, you and your healthcare provider should record the Benlysta lot number. It is recommended that you make a note of this information in case you are asked for it in the future.

Storage

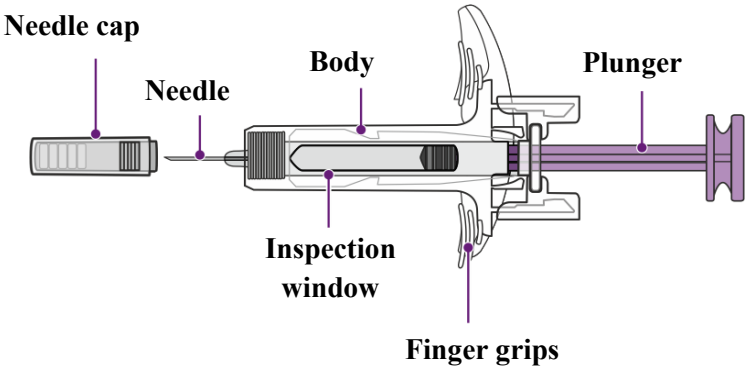
- Keep refrigerated until 30 minutes before use.
- Keep in the carton in order to protect from light.
- Keep out of the sight and reach of children.
- Keep away from heat and sunlight.
- **Do not** freeze. If the pre-filled syringe has been frozen, **do not** use the pre-filled syringe even if it is thawed.
- **Do not** use and **do not** place back in the refrigerator if left out at room temperature for more than 12 hours.

Warnings

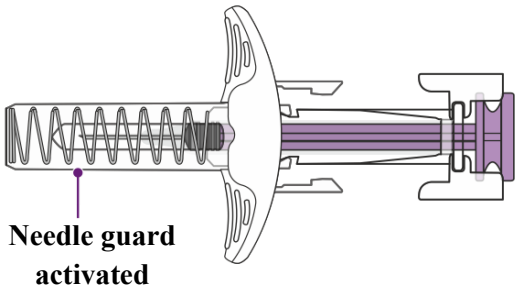
- The pre-filled syringe must only be used once and then discarded.
- **Do not** share your Benlysta pre-filled syringe with another person.
- **Do not** shake.
- **Do not** use if dropped onto a hard surface.
- **Do not** remove the needle cap until just before the injection.

Benlysta pre-filled syringe parts

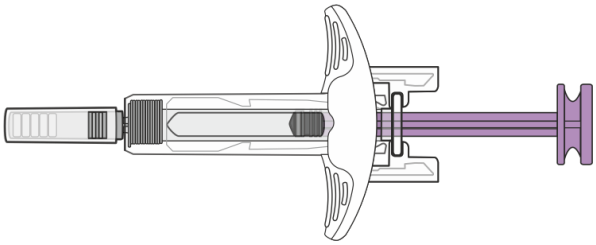
Before use



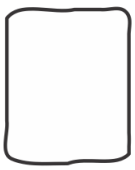
After use — needle is covered by needle guard



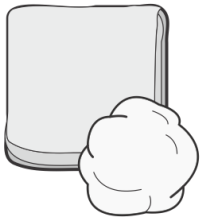
Supplies you need for the injection



Benlysta pre-filled syringe



Alcohol swab
(not included)



Gauze pad or cotton wool ball
(not included)

1. Gather and check supplies

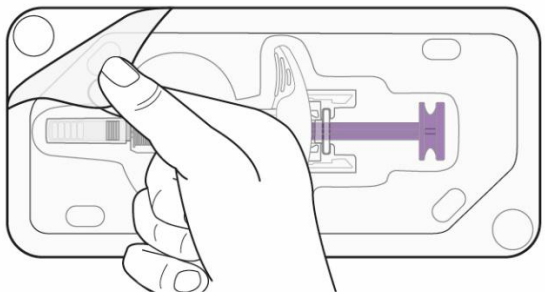
Gather supplies

- Remove one sealed tray containing a pre-filled syringe from the refrigerator.
- Place any remaining pre-filled syringes back into the refrigerator.
- Find a comfortable, well-lit and clean surface and place the following supplies within reach:
  - Benlysta pre-filled syringe
  - alcohol swab *(not included in the pack)*
  - gauze pad or cotton wool ball *(not included in the pack)*
  - container with a tight-fitting lid for syringe disposal *(not included in the pack)*.
- **Do not** perform the injection if you do not have all the supplies listed.

Take out the syringe

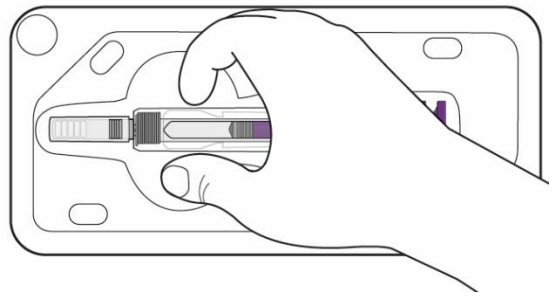
- Peel back the film from the corner of the tray. (*Figure 1*)

Figure 1



- Holding the middle of the pre-filled syringe (near the inspection window), carefully take the pre-filled syringe out of the tray. (*Figure 2*)

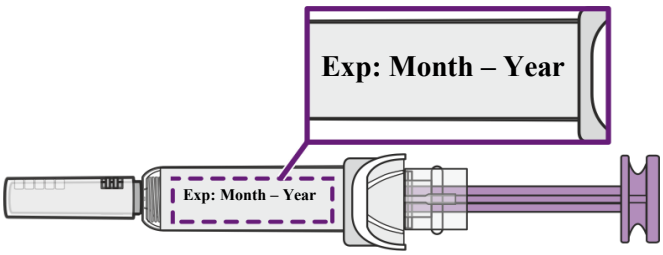
Figure 2



Check the expiry date

- Check the expiry date on the pre-filled syringe. (*Figure 3*)

Figure 3



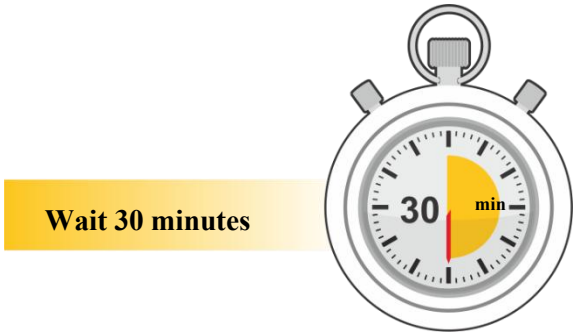
- **Do not** use if the expiry date has passed.

2. Prepare and inspect the pre-filled syringe

Allow to come to room temperature

- Leave the syringe at room temperature for 30 minutes. (*Figure 4*) Injecting cold Benlysta may take longer and may be uncomfortable.

Figure 4



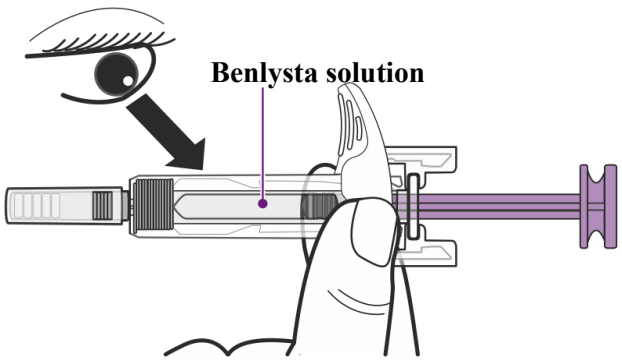
- **Do not** warm the syringe in any other way. For example, do not warm it in a microwave oven, hot water or direct sunlight.

- **Do not** remove the needle cap during this step.

Inspect the Benlysta solution

- Look in the inspection window to check that the Benlysta solution is colourless to slightly yellow in colour. (*Figure 5*)
    - It is normal to see one or more air bubbles in the solution.

Figure 5



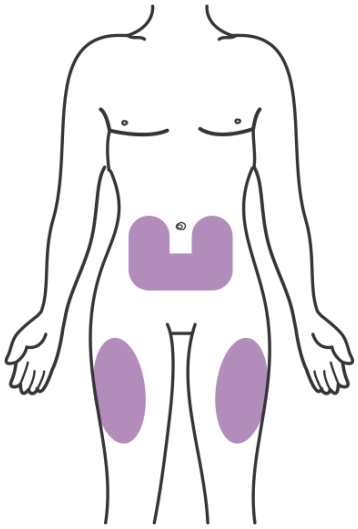
- **Do not** use if the solution looks cloudy, discoloured or has particles.

3. Choose and clean the injection site

Choose the injection site

- Choose an injection site (abdomen or thigh) as seen in *Figure 6*.

Figure 6

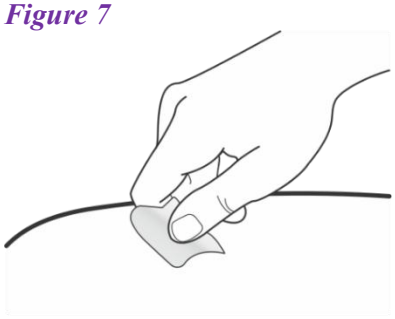


- If you need 2 injections to complete your dose, leave at least 5 cm (2 inches) between each injection if using the same site.
- **Do not** inject into the exact same site each time. This is to avoid the skin becoming hardened.
- **Do not** inject in areas where the skin is tender, bruised, red or hard.
- **Do not** inject within 5 cm (2 inches) of the navel (belly button).

Clean the injection site

- Wash your hands.
- Clean the injection site by wiping it with an alcohol swab (*Figure 7*). Allow the skin to air dry.

Figure 7



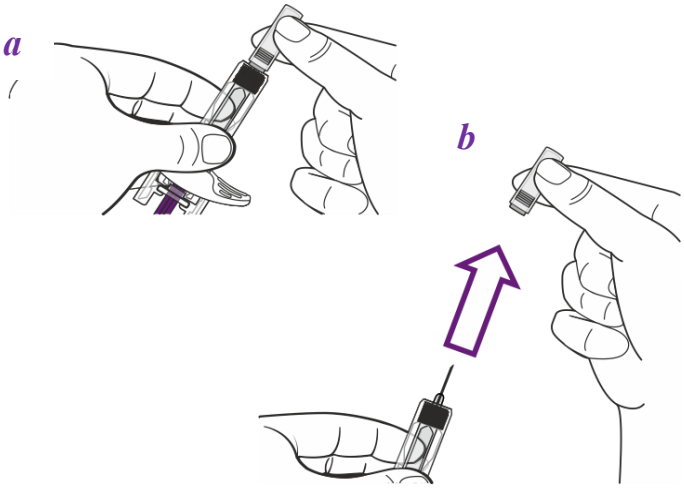
- **Do not** touch this area again before giving the injection.

4. Prepare for the injection

Remove the needle cap

- **Do not** remove the needle cap until immediately before the injection.
- Hold the pre-filled syringe by the body, and with the needle facing away from you. *(Figure 8a)*
- Remove the needle cap by pulling it straight off. (*Figure 8b*)

Figure 8



- You may see a drop of liquid at the end of the needle. This is normal.

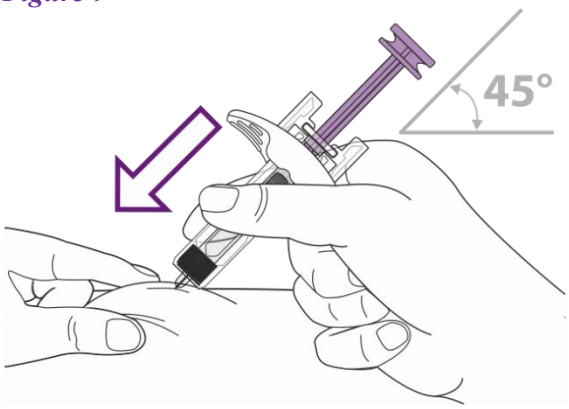
- **Do not** let the needle touch any surface.
- **Do not** expel any air bubbles from the syringe.
- **Do not** put the needle cap back onto the syringe.

5. Inject Benlysta and inspect

Insert the needle

- Hold the syringe in one hand.
- Use your free hand to gently pinch the skin around the injection site. (*Figure 9*)
- Insert the entire needle into the pinched area of the skin at a slight angle (45°), using a dart-like motion.

Figure 9

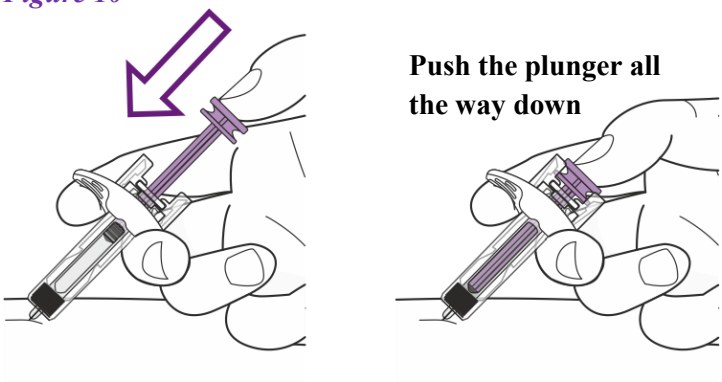


- After the needle is completely inserted, release the pinched skin.

Complete the injection

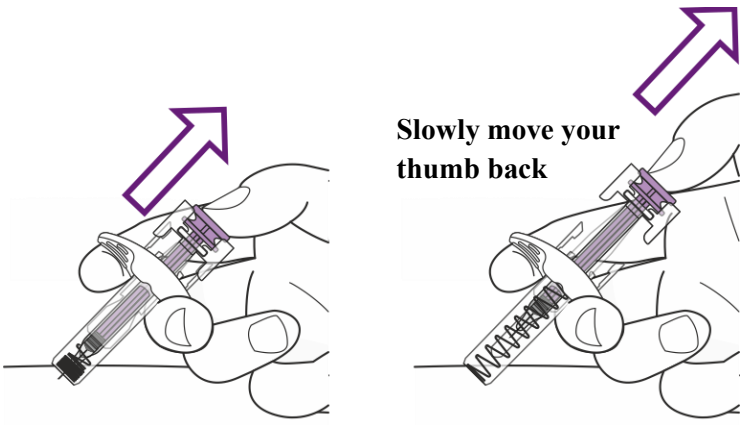
- Push the plunger all the way down until all of the solution is injected. (*Figure 10*)

Figure 10



- Keeping hold of the syringe, slowly move your thumb back, allowing the plunger to rise up (*Figure 11*).
    - The needle will automatically rise up into the needle guard.

Figure 11



Inspect the injection site

There may be a small amount of blood at the injection site.

- If needed, press a cotton ball or gauze pad on the injection site.
- **Do not** rub the injection site.

6. Dispose of used syringe

Dispose of the used syringe

- Dispose of the used syringe and needle cap in a container with a tight-fitting lid.

- Ask your doctor or pharmacist for instructions on how to properly dispose of a used syringe or container of used syringes.

- **Do not** recycle or throw the used syringe, or the container of used syringes in household waste.

Package leaflet: Information for the user

Benlysta 120 mg powder for concentrate for solution for infusion
Benlysta 400 mg powder for concentrate for solution for infusion
belimumab

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Benlysta is and what it is used for

Benlysta as an infusion is a medicine used to treat lupus (systemic lupus erythematosus, SLE) in adults and children (5 years of age and older) whose disease is still highly active despite standard treatment. Benlysta is also used in combination with other medicines to treat adults (18 years of age and older) with active lupus nephritis (lupus-related kidney inflammation).

Lupus is a disease in which the immune system (the system that fights infection) attacks your own cells and tissues, causing inflammation and organ damage. It can affect almost any organ in the body, and is thought to involve a type of white blood cells called *B cells*.

Benlysta contains **belimumab** (*a monoclonal antibody*). It reduces the number of B cells in your blood by blocking the action of BLyS, a protein that helps B cells to live longer and is found in high levels in people with lupus.

You will be given Benlysta as well as your usual treatment for lupus.

2. What you need to know before you are given Benlysta

Do not receive Benlysta

- if you are **allergic** to belimumab or any of the other ingredients of this medicine (listed in section 6).
  ➔ **Check with your doctor** if this may apply to you.

Warnings and precautions
Talk to your doctor before you are given Benlysta

- if you have a current or long-term **infection** or if you often get infections (see section 4). Your doctor will decide if you can be given Benlysta
- if you are planning to have a **vaccination** or have had a vaccination within the last 30 days. Some vaccines should not be given just before or during treatment with Benlysta
- if your lupus **affects your nervous system**
- if you are **HIV positive** or have **low immunoglobulin** levels
- if you have, or have had, **hepatitis B or C**
- if you have had an **organ transplant** or a **bone marrow** or **stem cell transplant**
- if you have had **cancer**.
- if you have ever developed a **severe skin rash** or **skin peeling**, **blistering** and/or **mouth sores** after using Benlysta.

➔ **Tell your doctor** if any of these may apply to you.

Depression and suicide
There have been reports of depression, suicidal thoughts, and suicide attempts including suicide during treatment with Benlysta. Tell your doctor if you have a history of these conditions. If you experience new or worsening symptoms at any time:

➔ **Contact your doctor or go to a hospital straight away**.

If you feel depressed or have thoughts of harming yourself or committing suicide, you may find it helpful to tell a relative or close friend and ask them to read this leaflet. You might ask them to tell you if they are worried about changes in your mood or behaviour.

Severe skin reactions
Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported in association with Benlysta treatment.

➔ **Stop using Benlysta and seek medical attention immediately if you notice any of the symptoms described in section 4.**

Look out for important symptoms
People taking medicines that affect their immune system may be more at risk of infections, including a rare but serious brain infection called *progressive multifocal leukoencephalopathy* (PML).

➔ **Read the information 'Increased risk of brain infection' in section 4 of this leaflet**.

To improve the traceability of this medicine, your healthcare provider should record the Benlysta lot number in your patient file. You may also wish to make a note of this information in case you are asked for it in the future.

Children and adolescents
This medicine is not intended for use in:

- children younger than 5 years of age with SLE
- children and adolescents (younger than 18 years of age) with active lupus nephritis.

Other medicines and Benlysta

Tell your doctor if you are taking any other medicines, if you have recently taken or might take any other medicines.

In particular tell your doctor if you are being treated with medicines that affect your immune system, including any medicine that affects your B cells (to treat cancer or inflammatory diseases).

Using such medicines in combination with Benlysta may make your immune system less effective. This could increase your risk of a serious infection.

Pregnancy and breast-feeding

Contraception for women who could become pregnant

- **Use an effective method of contraception** while you are being treated with Benlysta and for at least 4 months after the last dose.

Pregnancy

Benlysta is not usually recommended if you are pregnant.

- **Tell your doctor if you are pregnant,** think you may be pregnant, or are planning to have a baby. Your doctor will decide if you can be given Benlysta.
- **If you become pregnant** while being treated with Benlysta, tell your doctor.

Breast-feeding

Tell your doctor if you are breast-feeding. It is likely that Benlysta can pass into breast milk. Your doctor will discuss with you whether you should stop treatment with Benlysta while you are breast-feeding, or if you should stop breast-feeding.

Driving and using machines
Benlysta can have side effects which may make you less able to drive or use machines.

Benlysta contains polysorbate 80
Benlysta 120 mg powder for concentrate for solution for infusion: This medicine contains 0.6 mg of polysorbate 80 in each vial.

Benlysta 400 mg powder for concentrate for solution for infusion: This medicine contains 2.0 mg of polysorbate 80 in each vial.

Polysorbates may cause allergic reactions. Tell your doctor if you have or your child has any known allergies.

Benlysta contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per dose, so it is essentially sodium-free. However, before Benlysta is given to you or your child, it is mixed with a solution that contains sodium. Talk to your doctor if you or your child are on a low salt diet.

3. How Benlysta is used

A nurse or doctor will give you Benlysta through a drip in your vein (intravenous infusion) over one hour.

Adults and children (5 years of age and older)
Your doctor will decide on the correct dose depending on your body weight. The recommended dose is 10 mg for each kilogram (kg) of your body weight.

You are usually given Benlysta on the first day of treatment then again 14 and 28 days later. After this, Benlysta is usually given once every 4 weeks.

Medicine given before an infusion
Your doctor may decide to give you medicines which help to reduce any infusion reactions before you are given Benlysta. These may include a type of medicine called an anti-histamine and a medicine to prevent a high temperature. You will be checked closely and if you do have any reactions these will be treated.

Stopping treatment with Benlysta
Your doctor will decide if you need to stop being given Benlysta.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Stop using Benlysta and seek medical attention immediately if you notice any of the following symptoms of a severe skin reaction:
- reddish patches on the trunk, the patches are target-like macules or circular, often with central blisters, skin peeling, ulcers of mouth, throat, nose, genitals and eyes. These severe skin rashes can be preceded by fever and flu-like symptoms (Stevens-Johnson syndrome and toxic epidermal necrolysis). These side effects have been reported with unknown frequency (cannot be estimated from the available data).

Allergic reactions — get medical help immediately
Benlysta can cause a reaction to the infusion, or an allergic (*hypersensitivity*) reaction.
These are common side effects (may affect up to 1 in 10 people). They can occasionally be severe (uncommon, affecting up to 1 in 100 people), and could be life-threatening. These severe reactions are more likely to happen on the day of your first or second treatment with Benlysta, but can be delayed and occur several days afterwards.

Tell your doctor or nurse immediately, or go to the Emergency department of your nearest hospital, if you get any of the following symptoms of an allergic or infusion reaction:
- swelling of the face, lips, mouth or tongue
- wheezing, difficulty in breathing or shortness of breath
- rash
- itchy raised bumps or hives.

Rarely, less severe delayed reactions to Benlysta can also occur, usually 5 to 10 days after an infusion. They include symptoms such as rash, feeling sick, tiredness, muscle aches, headache, or facial swelling.
If you experience these symptoms, particularly if you get two or more of them together:
➔ **Tell your doctor or nurse.**

Infections
Benlysta can make you more likely to get infections, including infection of the urinary tract and airways, younger children may be at increased risk. These are very common and may affect more than 1 in 10 people. Some infections can be severe and can uncommonly cause death.

If you get any of the following symptoms of an infection:
- fever and/or chills
- cough, breathing problems
- diarrhoea, vomiting
- burning sensation while passing urine; urinating often
- warm, red or painful skin or sores on your body.

➔ **Tell your doctor or nurse immediately.**

Depression and suicide
There have been reports of depression, suicidal thoughts, and suicide attempts during treatment with Benlysta. Depression can affect up to 1 in 10 people, suicidal thoughts and suicide attempts can affect up to 1 in 100 people. If you feel depressed, have thoughts about harming yourself or other distressing thoughts, or if you are depressed and notice that you feel worse or develop new symptoms:

➔ **Contact your doctor or go to a hospital straight away.**

Increased risk of brain infection
Medicines that weaken your immune system, such as Benlysta, may put you at higher risk of getting a rare but serious and life-threatening brain infection called *progressive multifocal leukoencephalopathy* (PML).

Symptoms of PML include:
- memory loss
- trouble in thinking
- difficulty with talking or walking
- loss of vision.

➔ **Tell your doctor immediately** if you have any of these symptoms, or similar problems that have lasted over several days.

If you already had these symptoms before you started treatment with Benlysta:
➔ **Tell your doctor immediately** if you notice any changes in these symptoms.

Other possible side effects:

Very common side effects
These may affect **more than 1 in 10** people:
- bacterial infections *(see 'Infections' above)*.

Common side effects
These may affect **up to 1 in 10** people:
- high temperature or fever
- itchy, bumpy rash (hives), skin rash
- low white blood cell count (can be seen in blood tests)
- nose, throat or stomach infection
- pain in hands or feet
- migraine
- feeling sick, diarrhoea.

Reporting of side effects
If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Benlysta

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label and carton after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2 °C to 8 °C).

Do not freeze.

Store in the original package in order to protect from light.

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

6. Contents of the pack and other information

What Benlysta contains

- The active ingredient is belimumab.
  Each 5 mL vial contains 120 mg belimumab.
  Each 20 mL vial contains 400 mg belimumab.
  After reconstitution, the solution contains 80 mg belimumab per mL.

- The other ingredients are citric acid monohydrate (E 330), sodium citrate (E 331), sucrose and polysorbate 80 (E 433). See section 2 for further information on polysorbate 80 and sodium content.

What Benlysta looks like and contents of the pack
Benlysta is supplied as a white to off-white powder for solution for infusion, in a glass vial with a siliconised rubber stopper and a flip-off aluminium seal.

There is 1 vial in each pack.

Marketing Authorisation Holder
GlaxoSmithKline (Ireland) Limited
12 Riverwalk
Citywest Business Campus
Dublin 24
Ireland

Manufacturer
GlaxoSmithKline Manufacturing S.P.A.
Strada Provinciale Asolana No. 90
I-43056 San Polo di Torrile
Parma
Italy

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
GlaxoSmithKline Pharmaceuticals s.a./n.v.
Tél/Tel: + 32 (0)10 85 52 00

България
GlaxoSmithKline Trading Services Limited
Тел.: + 359 80018205

Česká republika
GlaxoSmithKline s.r.o.
Tel: + 420 222 001 111
cz.info@gsk.com

Danmark
GlaxoSmithKline Pharma A/S
Tlf.: + 45 36 35 91 00
dk-info@gsk.com

Deutschland
GlaxoSmithKline GmbH & Co. KG
Tel.: + 49 (0)89 36044 8701
produkt.info@gsk.com

Lietuva
GlaxoSmithKline Trading Services Limited
Tel: + 370 80000334

Luxembourg/Luxemburg
GlaxoSmithKline Pharmaceuticals s.a./n.v.
Belgique/Belgien
Tél/Tel: + 32 (0) 10 85 52 00

Magyarország
GlaxoSmithKline Trading Services Limited
Tel.: + 36 80088309

Malta
GlaxoSmithKline Trading Services Limited
Tel: + 356 80065004

Nederland
GlaxoSmithKline BV
Tel: + 31 (0)33 2081100

Eesti
GlaxoSmithKline Trading Services Limited
Tel: + 372 8002640

Ελλάδα
GlaxoSmithKline Μονοπρόσωπη A.E.B.E.
Τηλ: + 30 210 68 82 100

España
GlaxoSmithKline, S.A.
Tel: + 34 900 202 700
es-ci@gsk.com

France
Laboratoire GlaxoSmithKline
Tél.: + 33 (0)1 39 17 84 44
diam@gsk.com

Hrvatska
GlaxoSmithKline Trading Services Limited
Tel:+ 385 800787089

Ireland
GlaxoSmithKline (Ireland) Limited
Tel: + 353 (0)1 4955000

Ísland
Vistor ehf.
Sími: +354 535 7000

Italia
GlaxoSmithKline S.p.A.
Tel: + 39 (0)45 7741111

Κύπρος
GlaxoSmithKline Trading Services Limited
Τηλ: + 357 80070017

Latvija
GlaxoSmithKline Trading Services Limited
Tel: + 371 80205045

Norge
GlaxoSmithKline AS
Tlf: + 47 22 70 20 00

Österreich
GlaxoSmithKline Pharma GmbH
Tel: + 43 (0)1 97075 0
at.info@gsk.com

Polska
GSK Services Sp. z o.o.
Tel.: + 48 (0)22 576 9000

Portugal
GlaxoSmithKline – Produtos Farmacêuticos, Lda.
Tel: + 351 21 412 95 00
FI.PT@gsk.com

România
GlaxoSmithKline Trading Services Limited
Tel: + 40 800672524

Slovenija
GlaxoSmithKline Trading Services Limited
Tel: + 386 80688869

Slovenská republika
GlaxoSmithKline Trading Services Limited
Tel: + 421 800500589

Suomi/Finland
GlaxoSmithKline Oy
Puh/Tel: + 358 (0)10 30 30 30

Sverige
GlaxoSmithKline AB
Tel: + 46 (0)8 638 93 00
info.produkt@gsk.com

This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.

The following information is intended for healthcare professionals only:

Instructions for use and handling – reconstitution, dilution and administration

In order to improve traceability of biological medicinal products, the tradename and the batch number of the administered product should be clearly recorded.

1) How to reconstitute Benlysta

Reconstitution and dilution needs to be carried out under aseptic conditions.

Allow 10 to 15 minutes for the vial to warm to room temperature (15 °C to 25 °C).

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

WARNING: The 5 mL and 20 mL vials are reconstituted with different volumes of diluent, see below:

120 mg vial

The 120 mg single-use vial of Benlysta is reconstituted with 1.5 mL of water for injection to yield a final concentration of 80 mg/mL belimumab.

400 mg vial

The 400 mg single-use vial of Benlysta is reconstituted with 4.8 mL of water for injection to yield a final concentration of 80 mg/mL belimumab.

Amount of Benlysta	Vial size	Volume of diluent	Final concentration
120 mg	5 mL	1.5 mL	80 mg/mL
400 mg	20 mL	4.8 mL	80 mg/mL

The stream of water for injection needs to 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 (15 °C to 25 °C) 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 water has been added, but it may take up to 30 minutes. Protect the reconstituted solution from sunlight.

If a mechanical reconstitution device is used to reconstitute Benlysta it must not exceed 500 rpm and the vial is not to be swirled for longer than 30 minutes.

2) Before diluting Benlysta

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.

120 mg vial

After reconstitution, a volume of 1.5 mL (corresponding to 120 mg belimumab) can be withdrawn from each 5 mL vial.

400 mg vial

After reconstitution, a volume of 5 mL (corresponding to 400 mg belimumab) can be withdrawn from each 20 mL vial.

3) How to dilute the solution for infusion

The reconstituted medicinal product is diluted to 250 mL with sodium chloride 9 mg/mL (0.9 %), sodium chloride 4.5 mg/mL (0.45 %), or Lactated Ringer's solution for infusion. For patients whose body weight is less than or equal to 40 kg, infusion bags with 100 mL of these diluents may be considered providing that the resulting belimumab concentration in the infusion bag does not exceed 4 mg/mL.

5 % glucose intravenous solutions are incompatible with Benlysta and must not be used.

From a 250 mL (or 100 mL) infusion bag or bottle of sodium chloride 9 mg/mL (0.9 %), sodium chloride 4.5 mg/mL (0.45 %), or Lactated Ringer's solution for infusion, 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, must be protected from direct sunlight and stored refrigerated at 2 °C to 8 °C. Solutions diluted in sodium chloride 9 mg/mL (0.9 %), sodium chloride 4.5 mg/mL (0.45 %), or Lactated Ringer's solution for infusion may be stored at 2 °C to 8 °C or room temperature (15 °C to 25 °C).

The total time from reconstitution of Benlysta to completion of infusion must not exceed 8 hours.

4) How to administer the diluted solution

Benlysta is infused over a 1 hour period.

Benlysta must not be infused concomitantly in the same intravenous line with other agents.
No incompatibilities between Benlysta and polyvinylchloride or polyolefin bags have been observed.
