

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Pre-filled pen

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

Pre-filled syringe

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

Belimumab is a human, IgG1 λ monoclonal antibody, produced in a mammalian cell line (NS0) by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in pre-filled pen (injection)
Solution for injection in pre-filled syringe (injection)

A clear to opalescent, colourless to pale yellow solution, with a pH of 6.

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).

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 should be 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

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

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

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

Transition from intravenous to subcutaneous administration

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

Special populations

Elderly

The efficacy and safety of Benlysta in the elderly has not been established. Data on patients ≥ 65 years are limited to $< 1.8\%$ of the studied population. Therefore, the use of Benlysta in elderly patients is not recommended unless the benefits are expected to outweigh the risks. In case administration of Benlysta to elderly patients is deemed necessary, 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

The safety and efficacy of Benlysta in children and adolescents (< 18 years of age) has not been established. No data are available.

Method of administration

The pre-filled pen or pre-filled syringe should be used for subcutaneous injection only. The recommended injection sites are the abdomen or thigh. When injecting in the same region, patients should be advised to use a different injection site each week; injections should never be given into areas where the skin is tender, bruised, red, or hard.

Comprehensive instructions for subcutaneous administration of Benlysta in a pre-filled pen or 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

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

- severe active central nervous system lupus
- severe active lupus nephritis (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 or cyclophosphamide

Benlysta has not been studied in combination with other B cell targeted therapy or intravenous cyclophosphamide. Caution should be exercised if Benlysta is co-administered with other B cell targeted therapy or cyclophosphamide.

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 should 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 should 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 should be instructed to seek immediate medical attention if they experience any of these symptoms. The package leaflet should be provided 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, including opportunistic infections. Severe infections, including fatal cases, have been reported in SLE patients receiving immunosuppressant therapy, including belimumab (see section 4.8). Physicians should exercise caution when considering the use of Benlysta in patients with severe or chronic infections or a history of recurrent infection. Patients who develop an infection while undergoing treatment with Benlysta should be monitored closely and careful consideration given to interrupting immunosuppressant therapy including belimumab until the infection is resolved. The risk of using Benlysta in patients with active or latent tuberculosis is unknown.

Progressive multifocal leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) has been reported with Benlysta treatment for SLE. Physicians should 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 should be considered. If PML is suspected, further dosing must be suspended until PML has been excluded.

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 should be exercised 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.

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 should 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. No formal studies have been conducted. 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 every 2 weeks.

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

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. The clinical status of the subject and the adverse reaction profile of Benlysta should 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 3 placebo-controlled intravenous studies and 1 placebo-controlled subcutaneous study.

The data presented in the table below reflect exposure to Benlysta administered (10 mg/kg intravenously over a 1-hour period on Days 0, 14, 28, and then every 28 days for up to 52 weeks) in 674 patients with SLE, including 472 exposed for at least 52 weeks, and 556 patients exposed to 200 mg Benlysta subcutaneously once weekly for up to 52 weeks. The safety data presented include data beyond Week 52 in some patients. Data from post-marketing reports are also included.

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

Adverse reactions were reported in 87% of Benlysta-treated patients and 90% of placebo-treated patients. The most frequently reported adverse reactions ($\geq 5\%$ of patients with SLE treated with Benlysta plus standard of care and at a rate $\geq 1\%$ greater than placebo) were viral upper respiratory tract infections, bronchitis, and diarrhoea. The proportion of patients who discontinued treatment due to adverse reactions was 7% for Benlysta-treated patients and 8% for placebo-treated patients.

Tabulated 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	≥1/1,000 to <1/100
Rare	≥1/10,000 to <1/1000

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 reaction(s)
Infections and infestations	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*
	Uncommon	Anaphylactic reaction
	Rare	Delayed-type, non-acute hypersensitivity reactions
Psychiatric disorders	Common	Depression
Nervous system disorders	Common	Migraine
Gastrointestinal disorders	Very common	Diarrhoea, nausea
Skin and subcutaneous tissue disorders	Common	Injection site reactions**
	Uncommon	Angioedema, urticaria, rash
Musculoskeletal and connective tissue disorders	Common	Pain in extremity
General disorders and administration site conditions	Common	Infusion or injection-related systemic reactions*, pyrexia

*‘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 reactions in all cases.

**Applies to subcutaneous formulation only.

Description of selected adverse reactions

Data presented below are pooled from the intravenous clinical trials (10 mg/kg intravenous dose only) and the subcutaneous clinical trial.

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 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.

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

Psychiatric disorders: The incidence of depression reported as an adverse event was 3% in both groups receiving Benlysta or placebo.

Injection site reactions: In the subcutaneous trial, 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.

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Selective immunosuppressants, ATC code: L04AA26

Mechanism of action

Belimumab is a human IgG1 λ 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 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 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 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.

Immunogenicity

In the subcutaneous study where serum samples from more than 550 patients with SLE were tested, no anti-belimumab antibodies were detected during or after treatment with belimumab 200 mg subcutaneously.

Clinical efficacy and safety

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 $\geq 1:80$ 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.

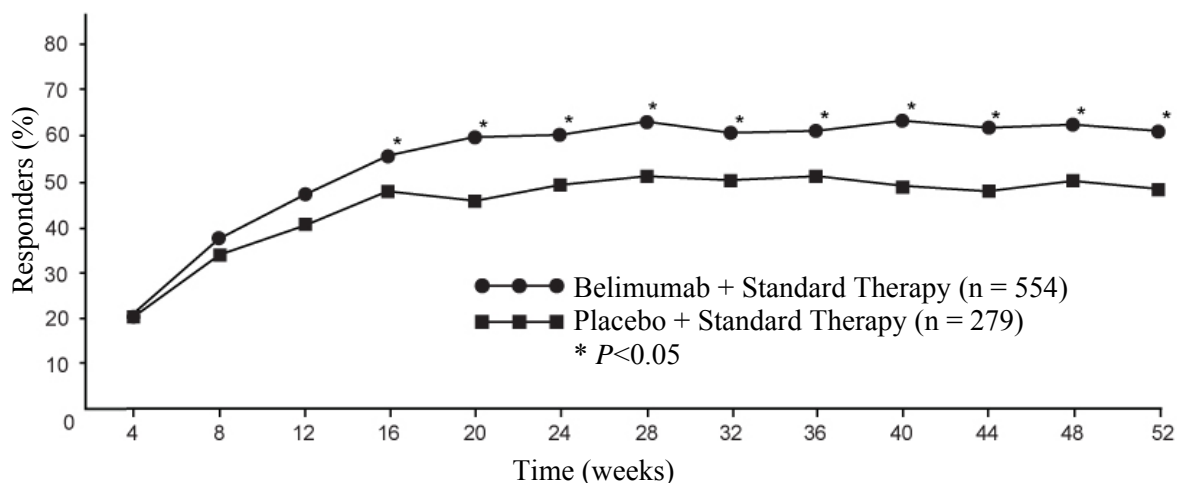
Table 1: Response rate at week 52

Response	Placebo (n=279)	Benlysta 200 mg weekly (n=554)
SLE responder index	48.4%	61.4% (p=0.0006)
Observed difference vs placebo		12.98%
Odds ratio (95% CI) vs placebo		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)

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 (%)	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 $\geq 25\%$ from baseline to ≤ 7.5 mg/day during weeks 24 through 52* (%)	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

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

Age and race

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

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Benlysta in one or more subsets of the paediatric population in SLE (see section 4.2 for information on paediatric use).

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 pre-filled pen or 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 (V_{ss}) 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.

Special Patient Populations

Paediatric population: No pharmacokinetic data are available in paediatric patients.

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 were not considered clinically meaningful. There was no significant impact on efficacy and safety based on weight. Therefore, no dose adjustment is recommended.

Transitioning from intravenous to subcutaneous administration

SLE patients transitioning from 10 mg/kg intravenously every 4 weeks to 200 mg subcutaneously weekly using a 1 to 4 week switching interval had pre-dose belimumab serum concentrations at their first subcutaneous dose close to their eventual subcutaneous steady-state trough concentration (see section 4.2).

Based on simulations with population PK parameters the steady-state average belimumab concentrations for 200 mg subcutaneous every week were similar to 10 mg/kg intravenous every 4 weeks.

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 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. 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
Sodium chloride
Water for injections

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.

6.5 Nature and contents of container

Pre-filled pen

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.

Pre-filled syringe

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 pen or 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

Glaxo Group Limited
980 Great West Road
Brentford
Middlesex TW8 9GS
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

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)
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 <http://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, IgG1 λ monoclonal antibody, produced in a mammalian cell line (NS0) by recombinant DNA technology.

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 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).

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 should 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 should be administered in an environment where resources for managing such reactions are immediately available. Patients should 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 should 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 should 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).

The recommended dose regimen is 10 mg/kg Benlysta on Days 0, 14 and 28, and at 4-week intervals thereafter. The patient's condition should be evaluated continuously. Discontinuation of treatment with Benlysta should be considered if there is no improvement in disease control after 6 months of treatment.

Transition from intravenous to subcutaneous administration

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

Special populations

Elderly

The efficacy and safety of Benlysta in the elderly has not been established. Data on patients ≥ 65 years are limited to <1.8% of the studied population. Therefore, the use of Benlysta in elderly patients is not recommended unless the benefits are expected to outweigh the risks. In case administration of Benlysta to elderly patients is deemed necessary, 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

The safety and efficacy of Benlysta in children and adolescents (<18 years of age) has 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 should 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

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

- severe active central nervous system lupus
- severe active lupus nephritis (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 or cyclophosphamide

Benlysta has not been studied in combination with other B cell targeted therapy or intravenous cyclophosphamide. Caution should be exercised if Benlysta is co-administered with other B cell targeted therapy or cyclophosphamide.

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 should 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 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 should be administered in an environment where resources for managing such reactions are immediately available. Patients should 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 should 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 should be instructed to seek immediate medical attention if they experience any of these symptoms. The package leaflet should 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, including opportunistic infections. Severe infections, including fatal cases, have been reported in SLE patients receiving immunosuppressant therapy, including belimumab (see section 4.8). Physicians should exercise caution when considering the use of Benlysta in patients with severe or chronic infections or a history of recurrent infection. Patients who develop an infection while undergoing treatment with Benlysta should be monitored closely and careful consideration given to interrupting immunosuppressant therapy including belimumab until the infection is resolved. The risk of using Benlysta in patients with active or latent tuberculosis is unknown.

Progressive multifocal leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) has been reported with Benlysta treatment for SLE. Physicians should 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 should be considered. If PML is suspected, further dosing must be suspended until PML has been excluded.

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 should be exercised 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.

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 should 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. No formal studies have been conducted. 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 every 2 weeks.

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

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. The clinical status of the subject and the adverse reaction profile of Benlysta should 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 3 placebo-controlled intravenous studies and 1 placebo-controlled subcutaneous study.

The data presented in the table below reflect exposure to Benlysta administered (10 mg/kg intravenously over a 1-hour period on Days 0, 14, 28, and then every 28 days for up to 52 weeks) in 674 patients with SLE, including 472 exposed for at least 52 weeks, and 556 patients exposed to 200 mg Benlysta subcutaneously once weekly for up to 52 weeks. The safety data presented include data beyond Week 52 in some patients. Data from post-marketing reports are also included.

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

Adverse reactions were reported in 87% of Benlysta-treated patients and 90% of placebo-treated patients. The most frequently reported adverse reactions ($\geq 5\%$ of patients with SLE treated with Benlysta plus standard of care and at a rate $\geq 1\%$ greater than placebo) were viral upper respiratory tract infections, bronchitis, and diarrhoea. The proportion of patients who discontinued treatment due to adverse reactions was 7% for Benlysta-treated patients and 8% for placebo-treated patients.

Tabulated list of adverse reactions

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

Very common	$\geq 1/10$
Common	$\geq 1/100$ to $< 1/10$
Uncommon	$\geq 1/1,000$ to $< 1/100$
Rare	$\geq 1/10,000$ to $< 1/1000$

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 reaction(s)
Infections and infestations	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*
	Uncommon	Anaphylactic reaction
	Rare	Delayed-type, non-acute hypersensitivity reactions
Psychiatric disorders	Common	Depression
Nervous system disorders	Common	Migraine
Gastrointestinal disorders	Very common	Diarrhoea, nausea
Skin and subcutaneous tissue disorders	Common	Injection site reactions**
	Uncommon	Angioedema, urticaria, rash
Musculoskeletal and connective tissue disorders	Common	Pain in extremity
General disorders and administration site conditions	Common	Infusion or injection-related systemic reactions*, pyrexia

*‘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 reactions in all cases.

**Applies to subcutaneous formulation only.

Description of selected adverse reactions

Data presented below are pooled from the intravenous clinical trials (10 mg/kg intravenous dose only) and the subcutaneous clinical trial.

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 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.

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

Psychiatric disorders: The incidence of depression reported as an adverse event was 3% in both groups receiving Benlysta or placebo.

Gastrointestinal disorders: Obese patients [Body mass index (BMI) >30 kg/m²] 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/m²). None of these gastrointestinal events in obese patients were serious.

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Selective immunosuppressants, ATC code: L04AA26

Mechanism of action

Belimumab is a human IgG1 λ 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 patients 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 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 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 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.

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 studies, 4 out of 563 (0.7%) patients in the 10 mg/kg group and 27 out of 559 (4.8%) patients in the 1 mg/kg group tested positive for persistent presence of anti-belimumab antibodies.

Among persistent-positive subjects in the Phase III studies, 1/10 (10%), 2/27 (7%) and 1/4 (25%) subjects in the placebo, 1 mg/kg and 10 mg/kg 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 and 10 mg/kg groups, respectively.

Clinical efficacy and safety

Intravenous infusion

The efficacy of Benlysta administered intravenously was evaluated in 2 randomized, double-blind, placebo-controlled studies in 1,684 patients with a clinical diagnosis of SLE according to the American College of Rheumatology classification criteria. Patients had active SLE disease, defined as a SELENA-SLEDAI (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 $\geq 1:80$ 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* (n=275)	Benlysta 10 mg/kg* (n=273)	Placebo* (n=287)	Benlysta 10 mg/kg* (n=290)	Placebo* (n=562)	Benlysta 10 mg/kg* (n=563)
SLE responder index	33.8%	43.2% (p=0.021)	43.6%	57.6% (p=0.0006)	38.8%	50.6% (p<0.0001)
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 \geq 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)

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

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

Age and race

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

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Benlysta in one or more subsets of the paediatric population in SLE (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

The intravenous pharmacokinetic parameters quoted below are based on population parameter estimates for the 563 patients who received Benlysta 10 mg/kg 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 $\mu\text{g/ml}$ (range: 173-573 $\mu\text{g/ml}$) 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 (V_{ss}) 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).

Special patient populations

Paediatric population: No pharmacokinetic data are available in paediatric patients.

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 PK modelling for patients at the midpoints of the renal impairment categories relative to patients with median creatinine clearance in the PK 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 10 mg/kg belimumab 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 transitioning from 10 mg/kg intravenously every 4 weeks to 200 mg subcutaneously weekly using a 1 to 4 week switching interval had pre-dose belimumab serum concentrations at their first subcutaneous dose close to their eventual subcutaneous steady-state trough concentration (see section 4.2). Based on simulations with population PK parameters the steady-state average belimumab concentrations for 200 mg subcutaneous every week were similar to 10 mg/kg intravenous every 4 weeks.

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 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. 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 (E330)
Sodium citrate (E331)
Sucrose
Polysorbate 80

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 injections, the reconstituted solution, if not used immediately, should 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 injection 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 should 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 aluminum 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 aluminum 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 injections to yield a final concentration of 80 mg/ml belimumab.

The stream of water for injections should be directed toward the side of the vial to minimize foaming. Gently swirl the vial for 60 seconds. Allow the vial to sit at room temperature (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 should not exceed 500 rpm and the vial should be swirled for no longer than 30 minutes.

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

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 injection.

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 injection, 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 should not exceed 8 hours.

Preparation of 400 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 400 mg single-use vial of belimumab is reconstituted with 4.8 ml of water for injections to yield a final concentration of 80 mg/ml belimumab.

The stream of water for injections should be directed toward the side of the vial to minimize foaming. Gently swirl the vial for 60 seconds. Allow the vial to sit at room temperature (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 should not exceed 500 rpm and the vial should be swirled for no longer than 30 minutes.

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

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 injection.

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 injection, 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 should not exceed 8 hours.

Method of administration

Benlysta is infused over a 1 hour period.

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

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

Disposal

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

7. MARKETING AUTHORISATION HOLDER

Glaxo Group Limited
980 Great West Road
Brentford
Middlesex TW8 9GS
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

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 <http://www.ema.europa.eu>.

ANNEX II

- A. MANUFACTURER OF THE BIOLOGICAL ACTIVE
SUBSTANCE AND MANUFACTURER(S) 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. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

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

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

OR

Glaxo Operations UK Ltd
Harmire Road
Barnard Castle
County Durham, DL12 8DT
United Kingdom

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**

The requirements for submission of periodic safety update reports 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 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
<p>The MAH shall provide the 1 year data report on a randomized, double-blind placebo-controlled large safety study, based on a protocol agreed with CHMP. The study will evaluate over a minimum of 1 year 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 non-serious and serious opportunistic infections and PML, malignancies (including non-melanoma skin cancer), serious infusion and hypersensitivity reactions, and serious psychiatric events including mood disorders, anxiety and suicide.</p>	<p>31 December 2019</p>
<p>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).</p>	<p>28 February 2026</p>

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(S)

Each 1 ml pre-filled pen contains 200 mg belimumab

3. LIST OF EXCIPIENTS

Also contains: arginine hydrochloride, histidine, histidine monohydrochloride, polysorbate 80, sodium chloride, water for injections.

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(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

Glaxo Group Ltd, 980 Great West Road, Brentford, Middlesex TW8 9GS, United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

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 LABEL – 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(S)

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

3. LIST OF EXCIPIENTS

Also contains: arginine hydrochloride, histidine, histidine monohydrochloride, polysorbate 80, sodium chloride, water for injections.

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(S) 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

Glaxo Group Ltd, 980 Great West Road, Brentford
Middlesex
TW8 9GS
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

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(S)

Each 1 ml pre-filled pen contains 200 mg belimumab

3. LIST OF EXCIPIENTS

Also contains: arginine hydrochloride, histidine, histidine monohydrochloride, polysorbate 80, sodium chloride, water for injections.

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(S) 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**

Glaxo Group Ltd, 980 Great West Road, Brentford
Middlesex
TW8 9GS,
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)**13. BATCH NUMBER**

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

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(S) 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(S)

Each 1 ml pre-filled syringe contains 200 mg belimumab

3. LIST OF EXCIPIENTS

Also contains: arginine hydrochloride, histidine, histidine monohydrochloride, polysorbate 80, sodium chloride, water for injections.

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(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

Glaxo Group Ltd, 980 Great West Road, Brentford, Middlesex TW8 9GS, United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

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(S) 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(S)

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

3. LIST OF EXCIPIENTS

Citric acid monohydrate (E330), sodium citrate (E331), sucrose, polysorbate 80

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

Glaxo Group Ltd, 980 Great West Road, Brentford, Middlesex TW8 9GS, United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

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:

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(S)

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

3. LIST OF EXCIPIENTS

Citric acid monohydrate (E330), sodium citrate (E331), sucrose, polysorbate 80

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

Glaxo Group Ltd, 980 Great West Road, Brentford, Middlesex TW8 9GS, United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

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(S) 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

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) 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
2. What you need to know before you use Benlysta
3. How Benlysta is used
4. Possible side effects
5. How to store Benlysta
6. Contents of the pack and other information
Step-by-step instructions for using the pre-filled pen

1. What Benlysta is and what it is used for

Benlysta 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.

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 **kidneys** or **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**.

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

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.**

Children and adolescents

Do not give this medicine to 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:

- cyclophosphamide (a medicine to treat some cancers and autoimmune disorders)
- any medicine that affects your B cells (to treat cancer or inflammatory diseases).

→ **Tell your doctor.** 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 in women of childbearing potential

- **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.

Important information about the contents of Benlysta

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

3. How Benlysta is used

How much to use

The recommended dose is 200 mg (complete contents of one pen) once a week, injected under your skin on the same day each 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 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).

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. It is not necessary to inject two doses on the same day.

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.

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
- cough, breathing problems
- diarrhoea, vomiting
- burning sensation while passing urine

→ Tell your doctor or nurse immediately.

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*)
- feeling sick, diarrhoea.

Common side effects

These may affect **up to 1 in 10** people:

- high temperature or fever
- low white blood cell count (can be seen in blood tests)
- nose, throat or stomach infection
- pain in hands or feet

- migraine
- depression
- injection site reactions, for example: rash, redness, itching or swelling of the skin where you have injected Benlysta.

Uncommon side effects

These may affect **up to 1 in 100** people:

- itchy, bumpy rash (hives), skin rash.

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.

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, sodium chloride, water for injections. See 'Important information about the contents of Benlysta' in section 2 for further information.

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.

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Manufacturer

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This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site:

<http://www.ema.europa.eu>.

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

Once-Weekly

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 should also receive training on how to use the pre-filled pen.

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

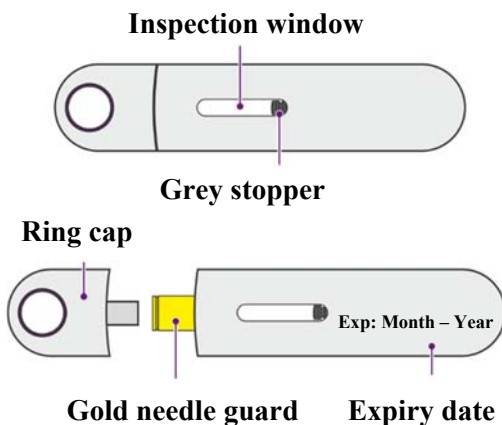
Storage

- 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.
- **Do not** freeze.
- **Do not** use if left out at room temperature for more than 12 hours.

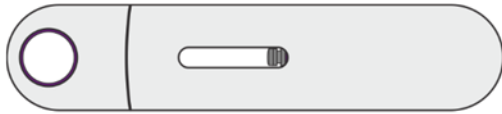
Warnings

- The pre-filled pen should be used only 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.

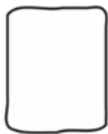
Benlysta pre-filled pen parts



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

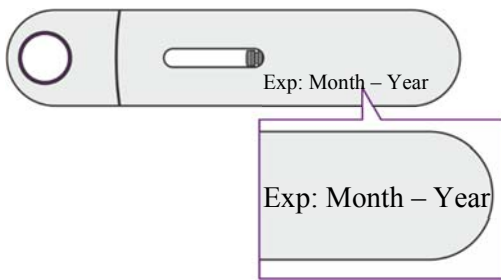
Gather supplies

- Remove one sealed tray containing a pre-filled pen from the refrigerator.
- 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)*
 - empty 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.

Check the expiry date

- Peel back the film of the tray and remove the pre-filled pen.
- Check the expiry date on the pre-filled pen. *(Figure 1)*

Figure 1



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 2*) Injecting cold Benlysta may take longer and may be uncomfortable.

Figure 2



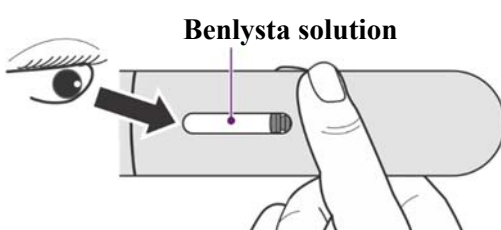
- **Do not** warm the pen in any other way. For example, do not warm it in a microwave oven, hot water or direct sunlight.
- **Do not** remove the ring cap during this step.

Inspect the Benlysta solution

- Look in the inspection window to check that the Benlysta solution is colourless to slightly yellow in colour. (*Figure 3*)

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

Figure 3



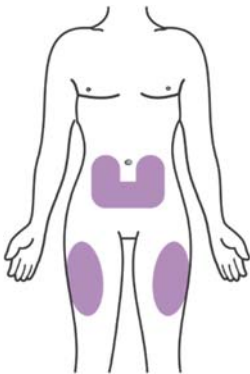
- **Do not** use if the solution looks cloudy, discoloured or has particles.

3. Choose and clean the injection site

Choose the injection site

- Choose an injection site (abdomen or thigh) as seen in *Figure 4*.

Figure 4



- **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 5*). Allow the skin to air dry.

Figure 5



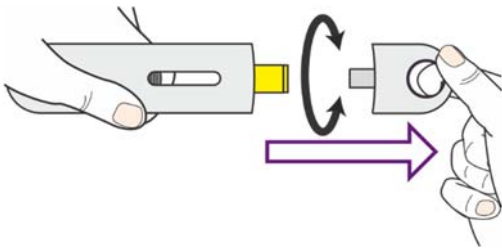
Do not touch this area again before giving the injection.

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 6*)

Figure 6

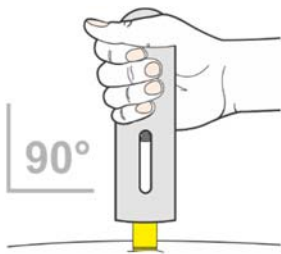


- **Do not** put the ring cap back onto the pen.

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 7*)

Figure 7



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

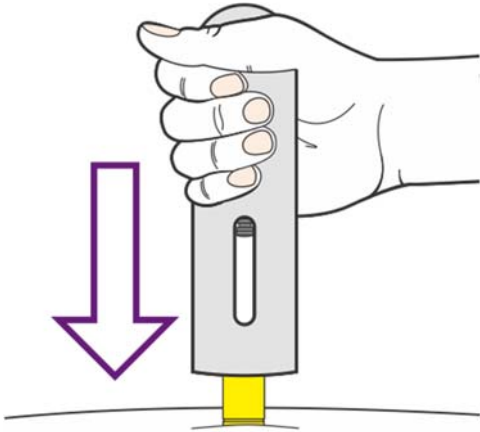
5. Inject Benlysta

Start the injection

- Firmly press the pen all the way down onto the injection site and hold in place. (*Figure 8*)

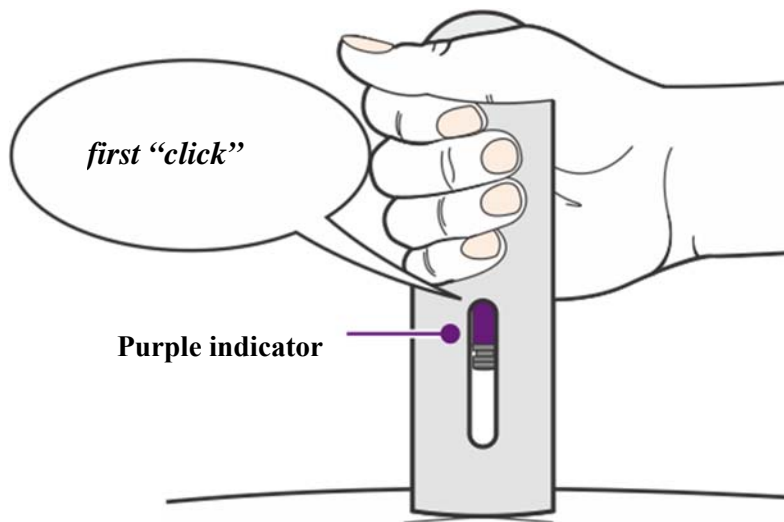
This will insert the needle and start the injection.

Figure 8



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 9*)

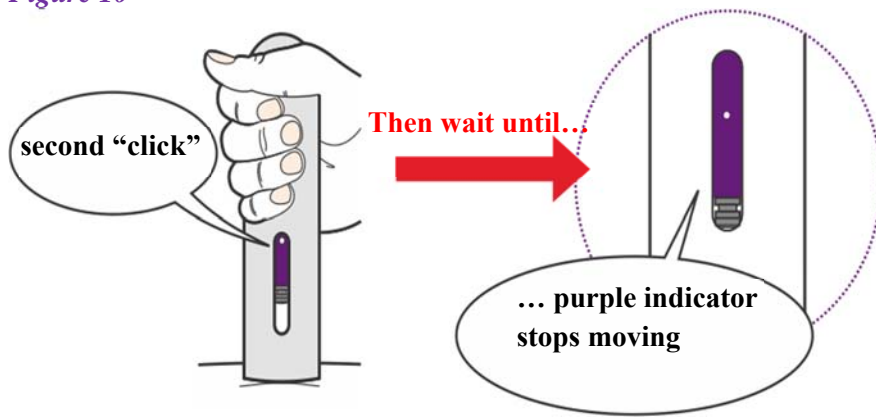
Figure 9



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 10*)

Figure 10



The injection may take up to 15 seconds to complete.

- When the injection is complete, lift the pen from the injection site.

6. Dispose and inspect

Dispose of the used pen

- Do not put the ring cap back onto the pen.
- Dispose of the used pen and ring cap in an empty 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 container of used pens, in household waste.

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.

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
2. What you need to know before you use Benlysta
3. How Benlysta is used
4. Possible side effects
5. How to store Benlysta
6. Contents of the pack and other information
Step-by-step instructions for using the pre-filled syringe

1. What Benlysta is and what it is used for

Benlysta 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.

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 **kidneys** or **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**.

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

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.**

Children and adolescents

Do not give this medicine to 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:

- cyclophosphamide (a medicine to treat some cancers and autoimmune disorders)
- any medicine that affects your B cells (to treat cancer or inflammatory diseases).

→ **Tell your doctor.** 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 in women of childbearing potential

- **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.

Important information about the contents of Benlysta

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

3. How Benlysta is used

How much to use

The recommended dose is 200 mg (complete contents of one syringe) once a week, injected under your skin on the same day each 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. It is not necessary to inject two doses on the same day.

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.

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
- cough, breathing problems
- diarrhoea, vomiting
- burning sensation while passing urine.

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

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*)
- feeling sick, diarrhoea.

Common side effects

These may affect **up to 1 in 10** people:

- high temperature or fever

- low white blood cell count (can be seen in blood tests)
- nose, throat or stomach infection
- pain in hands or feet
- migraine
- depression
- injection site reactions, for example: rash, redness, itching or swelling of the skin where you have injected Benlysta.

Uncommon side effects

These may affect **up to 1 in 100** people:

- itchy, bumpy rash (hives), skin rash.

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.

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, sodium chloride, water for injections. See 'Important information about the contents of Benlysta' in section 2 for further information.

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.

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Manufacturer

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This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site:

<http://www.ema.europa.eu>.

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

Once-Weekly

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 should also receive training on how to use the pre-filled syringe.

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

Storage

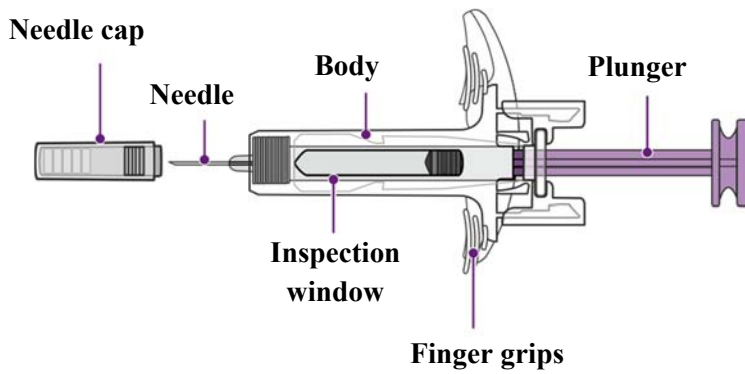
- Keep refrigerated until 30 minutes before use.
- Keep in the carton in order to protect from light.
- Keep out of the sight and reach of children.
- **Do not** freeze.
- **Do not** use if left out at room temperature for more than 12 hours.

Warnings

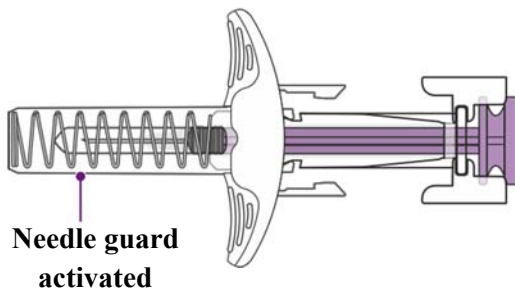
- The pre-filled syringe should be used only once and then discarded.
- **Do not** share your Benlysta pre-filled syringe with another person.
- **Do not** shake.
- **Do not** use if dropped onto a hard surface.
- **Do not** remove the needle cap until just before the injection.

Benlysta pre-filled syringe parts

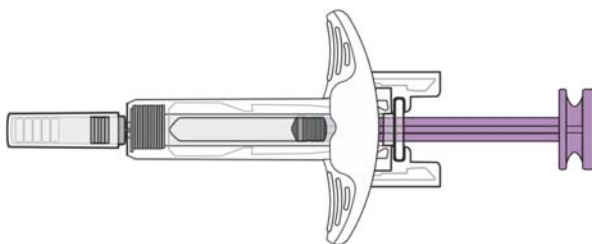
Before use



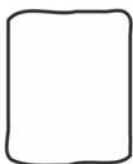
After use — needle is covered by needle guard



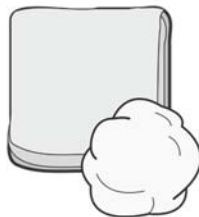
Supplies you need for the injection



Benlysta pre-filled syringe



Alcohol swab
(not included)



Gauze pad or cotton wool ball
(not included)

1. Gather and check supplies

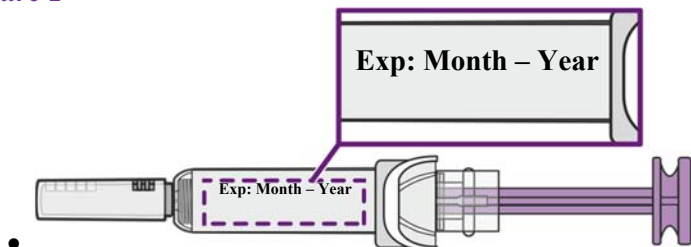
Gather supplies

- Remove one sealed tray containing a pre-filled syringe from the refrigerator.
- 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*)
 - empty 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.

Check the expiry date

- Peel back the film of the tray and remove the pre-filled syringe by grasping the middle of the body.
- Check the expiry date on the pre-filled syringe. (*Figure 1*)

Figure 1



- **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 2*) Injecting cold Benlysta may take longer and may be uncomfortable.

Figure 2



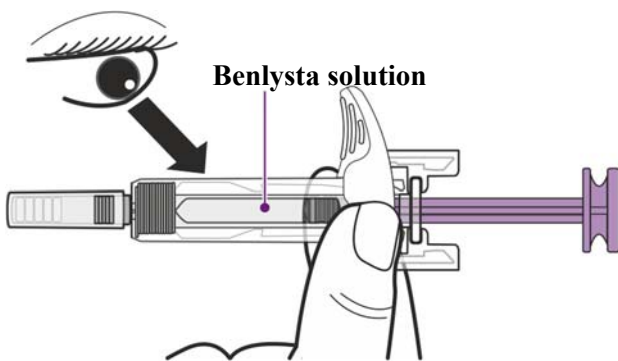
- **Do not** warm the syringe in any other way. For example, do not warm it in a microwave oven, hot water or direct sunlight.
- **Do not** remove the needle cap during this step.

Inspect the Benlysta solution

- Look in the inspection window to check that the Benlysta solution is colourless to slightly yellow in colour. (*Figure 3*)

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

Figure 3



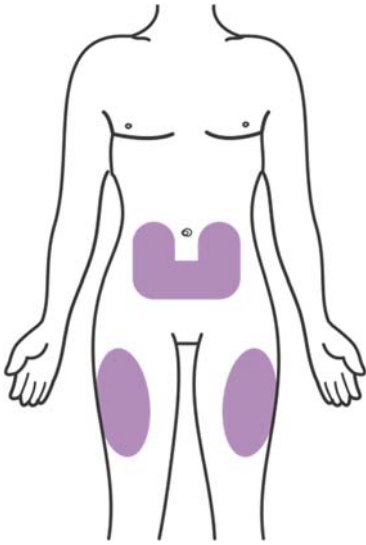
- **Do not** use if the solution looks cloudy, discoloured or has particles.

3. Choose and clean the injection site

Choose the injection site

- Choose an injection site (abdomen or thigh) as seen in *Figure 4*.

Figure 4



- **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 5*). Allow the skin to air dry.

Figure 5



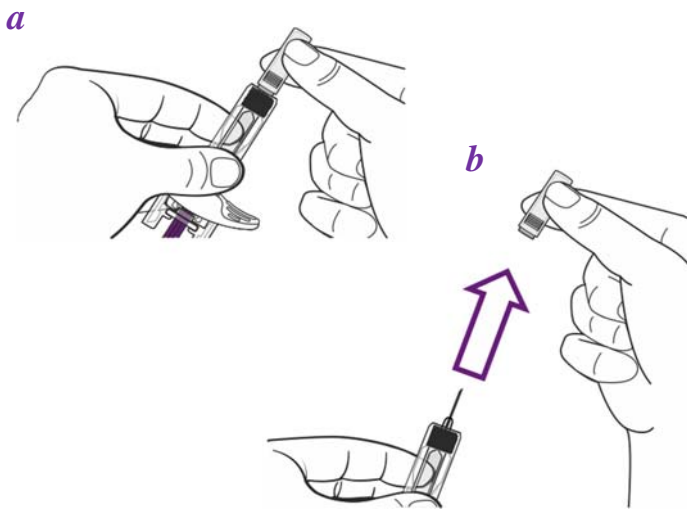
- **Do not** touch this area again before giving the injection.

4. Prepare for the injection

- **Do not** remove the needle cap until immediately before the injection.
- Hold the prefilled syringe by the body, and with the needle facing away from you. (*Figure 6a*)

- Remove the needle cap by pulling it straight off. (*Figure 6b*)

Figure 6



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

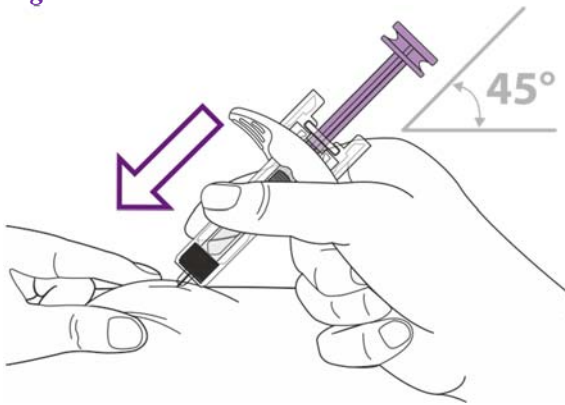
- **Do not** let the needle touch any surface.
- **Do not** expel any air bubbles from the syringe.
- **Do not** put the needle cap back onto the syringe.

5. Inject Benlysta

Insert the needle

- Hold the syringe in one hand.
- Use your free hand to gently pinch the skin around the injection site. (*Figure 7*)
- Insert the entire needle into the pinched area of the skin at a slight angle (45°), using a dart-like motion.

Figure 7

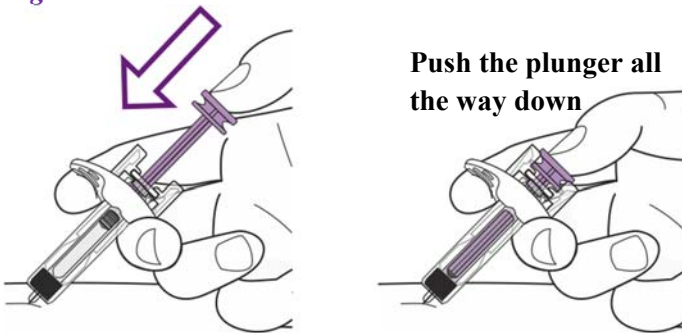


- After the needle is completely inserted, release the pinched skin.

Complete the injection

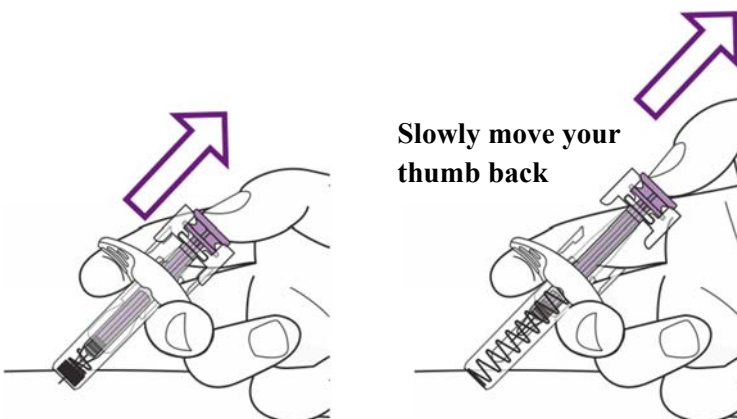
- Push the plunger all the way down until all of the solution is injected. (Figure 8)

Figure 8



Keeping hold of the syringe, slowly move your thumb back, allowing the plunger to rise up (Figure 9). The needle will automatically rise up into the needle guard.

Figure 9



6. Dispose and inspect

Dispose of the used syringe

- Dispose of the used syringe and needle cap in an empty 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 container of used syringes in household waste.

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.

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
2. What you need to know before you are given Benlysta
3. How Benlysta is used
4. Possible side effects
5. How to store Benlysta
6. Contents of the pack and other information

1. What Benlysta is and what it is used for

Benlysta 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.

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. 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 kidneys** or **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**.

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

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.**

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:

- cyclophosphamide (a medicine to treat some cancers and autoimmune disorders)
- any medicine that affects your B cells (to treat cancer or inflammatory diseases).

→ **Tell your doctor.** 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 in women of childbearing potential

- **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.

Important information about the contents of Benlysta

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

3. How Benlysta is used

A nurse or doctor will give you Benlysta through a drip in your vein (intravenous infusion) over one hour.

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.

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. 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
- cough, breathing problems
- diarrhoea, vomiting
- burning sensation while passing urine.

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

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*)
- feeling sick, diarrhoea.

Common side effects

These may affect **up to 1 in 10** people:

- high temperature or fever
- low white blood cell count (can be seen in blood tests)
- nose, throat or stomach infection
- pain in hands or feet
- migraine
- depression.

Uncommon side effects

These may affect **up to 1 in 100** people:

- itchy, bumpy rash (hives), skin rash.

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 (E330), sodium citrate (E331), sucrose and polysorbate 80. See 'Important information about the contents of Benlysta' in section 2 for further information.

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.

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This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site:

<http://www.ema.europa.eu>.

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The following information is intended for healthcare professionals only:

Instructions for use and handling – reconstitution, dilution and administration

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 injections 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 injections 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 injections should be directed toward the side of the vial to minimize foaming. Gently swirl the vial for 60 seconds. Allow the vial to sit at room temperature (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 should not exceed 500 rpm and the vial should be swirled for no longer than 30 minutes.

2) Before diluting Benlysta

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

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 injection.

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

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

The reconstituted solution, if not used immediately, should be protected from direct sunlight and stored refrigerated at 2°C to 8°C. Solutions diluted in sodium chloride 9 mg/ml (0.9%), sodium chloride 4.5 mg/ml (0.45%), or Lactated Ringer's solution for injection 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 should not exceed 8 hours.

4) How to administer the diluted solution

Benlysta is infused over a 1 hour period.

Benlysta should not be infused concomitantly in the same intravenous line with other agents.

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