

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 120 mg powder for concentrate for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 120 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 section 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).

There are no or insufficient data available on the effects of Benlysta in patients with severe active lupus nephritis or severe active central nervous system lupus. Therefore, Benlysta cannot be recommended to treat these conditions (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.

Special populations

Older people (>65 years)

The efficacy and safety of Benlysta in the elderly has not been established. Data on patients >65 years are limited to <1.6% 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 (less than 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 dyspnea. 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 section 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 the day 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 Benlysta could increase the potential risk for the development of infections, including opportunistic infections. Physicians should exercise caution when considering the use of Benlysta in patients with chronic infections or a history of recurrent infection. Patients receiving any therapy for chronic infection should not begin therapy with Benlysta. Patients who develop an infection while undergoing treatment with Benlysta should be monitored closely. 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. The efficacy of concurrent vaccination in patients receiving Benlysta is not known. Limited data suggest that Benlysta does not significantly affect the ability to maintain a protective immune response to immunisations received prior to administration of Benlysta. 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. There are insufficient data to draw conclusions regarding the ability of subjects receiving Benlysta to mount protective responses to vaccines.

Malignancies and lymphoproliferative disorders

Immunomodulatory medicinal products, including belimumab, may increase the risk of malignancy. Caution should be exercised when considering belimumab therapy for patients with a history of malignancy or when considering continuing treatment in patients who develop malignancy. 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.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

Women of child-bearing 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 clearly necessary.

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 Benlysta 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 Benlysta. 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 Benlysta in patients with SLE has been evaluated in 3 placebo-controlled studies. The data described below reflect exposure to Benlysta 10 mg/kg in 674 patients with SLE, including 472 exposed for at least 52 weeks. The safety data presented include data beyond Week 52 in some patients. Data from postmarketing reports are also included.

Patients received Benlysta 10 mg/kg intravenously over a 1-hour period on Days 0, 14, 28, and then every 28 days for 52 weeks.

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

Adverse reactions were reported in 93% of Benlysta-treated patients and 92% of placebo-treated patients. The most frequently reported adverse reactions ($\geq 10\%$ of patient with SLE treated with Benlysta plus standard of care and at a rate $\geq 1\%$ greater than placebo) were nausea, diarrhoea, and pyrexia. The proportion of patients who discontinued treatment due to adverse reactions was 7% for both Benlysta-treated and 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.

System organ class	Frequency	Adverse reaction(s)
Infections and infestations	Very common	Bacterial infections, e.g. bronchitis, cystitis
	Common	Gastroenteritis viral, pharyngitis, nasopharyngitis
Blood and lymphatic system disorders	Common	Leucopenia
Immune system disorders	Common	Hypersensitivity reactions*
	Uncommon	Anaphylactic reaction, angioedema
	Rare	Delayed-type, non-acute hypersensitivity reactions
Psychiatric disorders	Common	Depression, insomnia
Nervous system disorders	Common	Migraine
Gastrointestinal disorders	Very common	Diarrhoea, nausea
Skin and subcutaneous tissue disorders	Uncommon	Urticaria, rash
Musculoskeletal and connective tissue disorders	Common	Pain in extremity
General disorders and administration site conditions	Common	Infusion-related 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 dyspnea. 'Infusion-related 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.

Description of selected adverse reactions

Infusion reactions and hypersensitivity: The incidence of infusion reactions and hypersensitivity reactions occurring during or on the same day as an infusion was 17% in the group receiving Benlysta and 15% in the group receiving placebo, with 1% and 0.3%, respectively, requiring permanent treatment discontinuation. These reactions were generally observed on the day of infusion, but acute hypersensitivity reactions may also occur on the day after dosing. Patients with a history of multiple drug allergies or significant hypersensitivity reactions may be at increased risk.

Infections: The overall incidence of infections was 70% in the group receiving Benlysta and 67% in the group receiving placebo. Infections occurring in at least 3% of Benlysta patients and at least 1% more frequently than patients receiving placebo were nasopharyngitis, bronchitis, pharyngitis, cystitis, and gastroenteritis viral. Serious infections occurred in 5% of patients receiving Benlysta or placebo. Infections leading to discontinuation of treatment occurred in 0.6% of patients receiving Benlysta and 1% of patients receiving placebo. Opportunistic infections have been reported in patients treated with Benlysta.

Leucopenia: The incidence of leucopenia reported as an adverse event was 4% in the group receiving Benlysta and 2% in the group receiving placebo.

Psychiatric disorders: Insomnia occurred in 7% of the group receiving Benlysta and 5% of the group receiving placebo. Depression was reported in 5% and 4% of the groups receiving Benlysta and placebo, respectively.

Gastrointestinal disorders: Obese patients (BMI >30 kg/m²) treated with 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 no clinical experience with overdose of Benlysta.

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Selective immunosuppressants, ATC code: L04AA26

Mechanism of action

Benlysta is a human IgG1 λ monoclonal antibody specific for soluble human B Lymphocyte Stimulator protein (BLyS, also referred to as BAFF and TNFSF13B). Benlysta blocks the binding of soluble BLyS, a B cell survival factor, to its receptors on B cells. Benlysta does not bind B cells directly, but by binding BLyS, Benlysta 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. 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 19% of patients receiving placebo.

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).

In a long-term extension study, B cells (including naïve, activated, plasma cells and the SLE B cell subset) and IgG levels were followed for up to 172 weeks with ongoing belimumab treatment. A substantial and sustained decrease in various B cell subsets was observed leading to a 70% to 90% median reduction in naïve B cells, activated B cells and plasmacytoid cells, and up to 60% median reduction in plasma cells after 3 years of treatment. Over three years, a 20% to 30% median reduction in IgG levels was observed, with 0.5% of subjects experiencing a decrease in IgG levels to below 400 mg/dL. The impact of long-term B cell decrease on efficacy and safety has not yet been determined.

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

The efficacy of Benlysta 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 ≥ 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)

* plus standard therapy/standard of care

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

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

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

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

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).

Age and race

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

5.2 Pharmacokinetic properties

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

Distribution

Belimumab distributed to tissues with an overall volume of distribution of 5.29 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).

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

Older people (older than or equal to 65 years of age): 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 or older, 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 Benlysta. 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/BMI: Weight-normalised belimumab dosing leads to decreased exposure for underweight subjects (BMI <18.5) and to increased exposure for obese subjects (BMI \geq 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.

5.3 Preclinical safety data

Nonclinical 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 Benlysta treatment was not associated with direct or indirect harmful effects with respect to maternal toxicity, developmental toxicity, or teratogenicity. Treatment-related findings were limited to the expected reversible reduction of B cells in both dams and infants and reversible reduction of IgM in infant monkeys. B cell numbers recovered after the cessation of belimumab treatment by about 1 year post-partum in adult monkeys and by 3 months of life in infant monkeys; IgM levels in infants exposed to belimumab *in utero* recovered by 6 months of age.

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

Belimumab 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 - 8°C.

Reconstituted and diluted solution for infusion

Solution of Benlysta diluted in sodium chloride 9 mg/ml (0.9%) solution for injection may be stored at 2°C-8°C or room temperature (15°C - 25°C).

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

6.4 Special precautions for storage

Unopened vials

Store in a refrigerator (2°C - 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

Type 1 glass vials (5 ml), sealed with a latex-free, siliconised chlorobutyl rubber stopper and a flip-off aluminum seal.

Pack size: 1 vial

6.6 Special precautions for disposal and other handling

Preparation of the solution for infusion

Reconstitution

Reconstitution and dilution must be carried out under aseptic conditions.

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

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 - 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%) 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%) 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

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 13 July 2011

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 400 mg powder for concentrate for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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 section 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).

There are no or insufficient data available on the effects of Benlysta in patients with severe active lupus nephritis or severe active central nervous system lupus. Therefore, Benlysta cannot be recommended to treat these conditions (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.

Special populations

Older people (>65 years)

The efficacy and safety of Benlysta in the elderly has not been established. Data on patients >65 years are limited to <1.6% 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 (less than 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 dyspnea. 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 section 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 the day 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 Benlysta could increase the potential risk for the development of infections, including opportunistic infections. Physicians should exercise caution when considering the use of Benlysta in patients with chronic infections or a history of recurrent infection. Patients receiving any therapy for chronic infection should not begin therapy with Benlysta. Patients who develop an infection while undergoing treatment with Benlysta should be monitored closely. 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. The efficacy of concurrent vaccination in patients receiving Benlysta is not known. Limited data suggest that Benlysta does not significantly affect the ability to maintain a protective immune response to immunisations received prior to administration of Benlysta. 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. There are insufficient data to draw conclusions regarding the ability of subjects receiving Benlysta to mount protective responses to vaccines.

Malignancies and lymphoproliferative disorders

Immunomodulatory medicinal products, including belimumab, may increase the risk of malignancy. Caution should be exercised when considering belimumab therapy for patients with a history of malignancy or when considering continuing treatment in patients who develop malignancy. 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.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

Women of child-bearing 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 clearly necessary.

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 Benlysta 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 Benlysta. 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 Benlysta in patients with SLE has been evaluated in 3 placebo-controlled studies. The data described below reflect exposure to Benlysta 10 mg/kg in 674 patients with SLE, including 472 exposed for at least 52 weeks. The safety data presented include data beyond Week 52 in some patients. Data from postmarketing reports are also included.

Patients received Benlysta 10 mg/kg intravenously over a 1-hour period on Days 0, 14, 28, and then every 28 days for 52 weeks.

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

Adverse reactions were reported in 93% of Benlysta-treated patients and 92% of placebo-treated patients. The most frequently reported adverse reactions ($\geq 10\%$ of patient with SLE treated with Benlysta plus standard of care and at a rate $\geq 1\%$ greater than placebo) were nausea, diarrhoea, and pyrexia. The proportion of patients who discontinued treatment due to adverse reactions was 7% for both Benlysta-treated and 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.

System organ class	Frequency	Adverse reaction(s)
Infections and infestations	Very common	Bacterial infections, e.g. bronchitis, cystitis
	Common	Gastroenteritis viral, pharyngitis, nasopharyngitis
Blood and lymphatic system disorders	Common	Leucopenia
Immune system disorders	Common	Hypersensitivity reactions*
	Uncommon	Anaphylactic reaction, angioedema
	Rare	Delayed-type, non-acute hypersensitivity reactions
Psychiatric disorders	Common	Depression, insomnia
Nervous system disorders	Common	Migraine
Gastrointestinal disorders	Very common	Diarrhoea, nausea
Skin and subcutaneous tissue disorders	Uncommon	Urticaria, rash
Musculoskeletal and connective tissue disorders	Common	Pain in extremity
General disorders and administration site conditions	Common	Infusion-related 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 dyspnea. 'Infusion-related 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.

Description of selected adverse reactions

Infusion reactions and hypersensitivity: The incidence of infusion reactions and hypersensitivity reactions occurring during or on the same day as an infusion was 17% in the group receiving Benlysta and 15% in the group receiving placebo, with 1% and 0.3%, respectively, requiring permanent treatment discontinuation. These reactions were generally observed on the day of infusion, but acute hypersensitivity reactions may also occur on the day after dosing. Patients with a history of multiple drug allergies or significant hypersensitivity reactions may be at increased risk.

Infections: The overall incidence of infections was 70% in the group receiving Benlysta and 67% in the group receiving placebo. Infections occurring in at least 3% of Benlysta patients and at least 1% more frequently than patients receiving placebo were nasopharyngitis, bronchitis, pharyngitis, cystitis, and gastroenteritis viral. Serious infections occurred in 5% of patients receiving Benlysta or placebo. Infections leading to discontinuation of treatment occurred in 0.6% of patients receiving Benlysta and 1% of patients receiving placebo. Opportunistic infections have been reported in patients treated with Benlysta.

Leucopenia: The incidence of leucopenia reported as an adverse event was 4% in the group receiving Benlysta and 2% in the group receiving placebo.

Psychiatric disorders: Insomnia occurred in 7% of the group receiving Benlysta and 5% of the group receiving placebo. Depression was reported in 5% and 4% of the groups receiving Benlysta and placebo, respectively.

Gastrointestinal disorders: Obese patients (BMI >30 kg/m²) treated with 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 no clinical experience with overdose of Benlysta.

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Selective immunosuppressants, ATC code: L04AA26

Mechanism of action

Benlysta is a human IgG1 λ monoclonal antibody specific for soluble human B Lymphocyte Stimulator protein (BLyS, also referred to as BAFF and TNFSF13B). Benlysta blocks the binding of soluble BLyS, a B cell survival factor, to its receptors on B cells. Benlysta does not bind B cells directly, but by binding BLyS, Benlysta 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. 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 19% of patients receiving placebo.

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).

In a long-term extension study, B cells (including naïve, activated, plasma cells and the SLE B cell subset) and IgG levels were followed for up to 172 weeks with ongoing belimumab treatment. A substantial and sustained decrease in various B cell subsets was observed leading to a 70% to 90% median reduction in naïve B cells, activated B cells and plasmacytoid cells, and up to 60% median reduction in plasma cells after 3 years of treatment. Over three years, a 20% to 30% median reduction in IgG levels was observed, with 0.5% of subjects experiencing a decrease in IgG levels to below 400 mg/dL. The impact of long-term B cell decrease on efficacy and safety has not yet been determined.

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

The efficacy of Benlysta 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)

* plus standard therapy/standard of care

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 belimumab compared to the group receiving placebo (110 vs 84 days, hazard ratio=0.84, p=0.012). Severe flares were observed in 15.6% of the Benlysta group compared to 23.7% of the placebo group over the 52 weeks of observation (observed treatment difference = -8.1%; hazard ratio=0.64, p=0.0011).

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

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

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).

Age and race

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

5.2 Pharmacokinetic properties

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

Distribution

Belimumab distributed to tissues with an overall volume of distribution of 5.29 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).

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

Older people (older than or equal to 65 years of age): 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 or older, 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 Benlysta. 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/BMI: Weight-normalised belimumab dosing leads to decreased exposure for underweight subjects (BMI <18.5) and to increased exposure for obese subjects (BMI \geq 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.

5.3 Preclinical safety data

Nonclinical 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 Benlysta treatment was not associated with direct or indirect harmful effects with respect to maternal toxicity, developmental toxicity, or teratogenicity. Treatment-related findings were limited to the expected reversible reduction of B cells in both dams and infants and reversible reduction of IgM in infant monkeys. B cell numbers recovered after the cessation of belimumab treatment by about 1 year post-partum in adult monkeys and by 3 months of life in infant monkeys; IgM levels in infants exposed to belimumab *in utero* recovered by 6 months of age.

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

Belimumab 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 - 8°C.

Reconstituted and diluted solution for infusion

Solution of Benlysta diluted in sodium chloride 9 mg/ml (0.9%) solution for injection may be stored at 2°C - 8°C or room temperature (15°C - 25°C).

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

6.4 Special precautions for storage

Unopened vials

Store in a refrigerator (2°C - 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

Type 1 glass vials (20 ml), sealed with a latex-free, siliconised chlorobutyl rubber stopper and a flip-off aluminum seal.

Pack size: 1 vial

6.6 Special precautions for disposal and other handling

Preparation of the solution for infusion

Reconstitution

Reconstitution and dilution must be carried out under aseptic conditions.

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

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 - 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%) 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%) 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/1/11/700/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 13 July 2011

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

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 marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and 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.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

• **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

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 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

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

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 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

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

120 mg 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

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

400 mg VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT

Benlysta 400 mg powder for concentrate for solution for infusion
Belimumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

5. METHOD AND ROUTE OF ADMINISTRATION

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

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED 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.

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

12. MARKETING AUTHORISATION NUMBER(S)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

B. PACKAGE LEAFLET

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 over) 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

You must 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

Take special care with Benlysta:

Talk to your doctor before you are given Benlysta.

- if you have a long-term **infection** or if you often get infections. Your doctor will decide if you can be given Benlysta.
- if you are **planning to get vaccinated or have recently had a vaccination** (within the last 30 days). Certain types of vaccines should not be given just before or during treatment with Benlysta.
- if your lupus **affects your kidneys or nervous system;**
- **if you have** HIV or 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

Progressive multifocal leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) is a serious and life threatening brain infection. Your chance of getting PML may be higher if you are treated with medicines that weaken your immune system, including Benlysta.

Tell your doctor immediately if you have memory loss, trouble thinking, difficulty with talking or walking, loss of vision, or similar problems that have lasted over several days.

If you had these symptoms prior to treatment with Benlysta

Tell your doctor immediately about any changes in these symptoms.

Other medicines and Benlysta

Tell your doctor if you are being treated with cyclophosphamide (a medicine that affects your immune system, used to treat some cancers and autoimmune disorders) or a medicine that affects your B cells (used to treat cancer or inflammatory diseases). The combination of such medicines together with Benlysta may make your immune system less effective. This could increase your risk of a serious infection.

Tell your doctor if you are taking any other medicines, if you have recently taken any, or if you start to take any new ones. This includes medicines that you can get without a prescription.

Pregnancy and breast-feeding

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

If you are 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

The effect of Benlysta on your ability to drive or use machines is not known.

Benlysta contains:

Benlysta contains less than 23 mg of sodium in each dose and therefore 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.

Hypersensitivity reactions and infusion reactions

Benlysta can cause a reaction to the infusion or an allergic (hypersensitivity) reaction. These can affect 1 to 10 users in 100, and can occasionally be severe, and could be life-threatening. These reactions are more likely to happen on the day of, or day after, your first or second treatment with Benlysta.

If you get any of the following symptoms of a hypersensitivity or infusion reaction tell your doctor or nurse immediately or go to the casualty department at your nearest hospital;

- swelling of the face, lips, mouth or tongue
- wheezing, difficulty in breathing or shortness of breath
- rash
- itchy raised bumps or hives

Adverse reactions can also occur later with Benlysta, generally 5-10 days after a dose of medication and include a combination of symptoms such as rash, feeling sick, tiredness, muscle aches, headache, and/or facial swelling.

If you experience these symptoms, particularly if you experience a combination of such symptoms, tell your doctor or a nurse.

Very common side effects

These may affect more than 1 in 10 people:

- bacterial infections, such as chest or bladder infections
- feeling sick, diarrhoea

Common side effects

These may affect up to 1 in 10 people:

- high temperature or fever;
- low white blood cell count;
- nose, throat, or stomach infection;
- pain in hands or feet;
- migraine;
- sleeplessness, depression.

Uncommon side effects

These may affect up to 1 in 100 people:

- severe allergic reactions, sometimes with swelling of face or mouth causing difficulty in breathing;
- swelling of the face, lips and tongue;
- rash;
- itchy raised bumps or hives.

Tell your doctor or a nurse immediately if you get any of these symptoms.

If you get any side effects, talk to your doctor. This includes any possible side-effects not listed in this leaflet.

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 – 8°C).

Do not freeze.

Store in the original package 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.
- The other ingredients are citric acid monohydrate (E330), sodium citrate (E331), sucrose and polysorbate 80

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 latex-free, siliconised rubber stopper and a flip-off aluminium seal.

There is 1 vial in each pack.

Marketing Authorisation Holder

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

Manufacturer

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

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

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

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 - 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%) 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%) 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 -8°C. Solutions diluted in sodium chloride 9 mg/ml (0.9%) solution for injection may be stored at 2°C - 8°C or room temperature (15°C - 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.

See section 5 of this leaflet for instructions on how to store Benlysta.

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