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Benlysta120 mg
Benlysta 400 mg

1. NAME OF THE MEDICINAL PRODUCT

Benlysta 120 mg
Benlysta400 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Benlysta 120 mg:
Each vial contains 120 mg of belimumab. After reconstitution, the solution contains 80 mg belimumab per ml.

Benlysta 400 mg:
Each vial contains 400 mg of belimumab.

After reconstitution, the solution contains 80 mg belimumab per ml.

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

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

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

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

Posology

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

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

Transition from intravenous to subcutaneous administration

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

Special populations

Elderly
The efficacy and safety of Benlysta in the elderly has not been established. Data on patients ≥ 65 years are limited to <1. 8% of the studied population. Therefore, the use of Benlysta in elderly patients is not recommended unless the benefits are expected to outweigh the risks. In case administration of Benlysta to elderly patients is deemed necessary, dose adjustment is not required (see section 5.2).

Renal impairment
Belimumab has been studied in a limited number of SLE patients with renal impairment.
On the basis of the available information, dose adjustment is not required in patients with mild, moderate or severe renal impairment. Caution is however recommended in patients with severe renal impairment due to the lack of data (see section 5.2).

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

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

Method of administration

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

Benlysta should be infused over a 1-hour period.

Benlysta must not be administered as an intravenous bolus.

The infusion rate may be slowed or interrupted if the patient develops an infusion reaction. The infusion must be discontinued immediately if the patient experiences a potentially life-threatening adverse reaction (see sections 4.4 and 4.8).

4.3 Contraindications

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

4.4 Special warnings and precautions for use

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

- severe active central nervous system lupus
- severe active lupus nephritis (see section 5.1)
- HIV
- a history of, or current, hepatitis B or C
- hypogammaglobulinaemia (IgG <400 mg/dl) or IgA deficiency (IgA <10 mg/dl)
- a history of major organ transplant or hematopoietic stem /cell /marrow transplant or renal transplant.

Concomitant use with B cell targeted therapy or cyclophosphamide

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

Infusion reactions and hypersensitivity

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

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

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

be instructed to seek immediate medical attention if they experience any of these symptoms. The package leaflet should be provided to the patient each time Benlysta is administered (see section 4.2).

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

Infections

The mechanism of action of belimumab could increase the risk for the development of infections, including opportunistic infections. Severe infections, including fatal cases, have been reported in SLE patients receiving immunosuppressant therapy, including belimumab (see section 4.8). Physicians should exercise caution when considering the use of Benlysta in patients with severe or chronic infections or a history of recurrent infection.-Patients who develop an infection while undergoing treatment with Benlysta should be monitored closely and careful consideration given to interrupting immunosuppressant therapy including belimumab until the infection is resolved. The risk of using Benlysta in patients with active or latent tuberculosis is unknown.

Depression and suicidality

In controlled clinical intravenous and subcutaneous studies, psychiatric disorders (depression, suicidal ideation and behaviour including suicides) have been reported more frequently in patients receiving Benlysta (see section 4.8). Physicians should assess the risk of depression and suicide considering the patient's medical history and current psychiatric status before treatment with Benlysta and continue to monitor patients during treatment. Physicians should advise patients (and caregivers where appropriate) to contact their health care provider about new or worsening psychiatric symptoms. In patients who experience such symptoms, treatment discontinuation should be considered.

Progressive multifocal leukoencephalopathy

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

Immunisation

Live vaccines should not be given for 30 days before, or concurrently with Benlysta, as clinical safety has not been established. No data are available on the secondary transmission of infection from persons receiving live vaccines to patients receiving Benlysta.

Because of its mechanism of action, belimumab may interfere with the response to immunisations. However, in a small study evaluating the response to a 23-valent pneumococcal vaccine, overall immune responses to the different serotypes were similar in SLE patients receiving Benlysta compared with those receiving standard immunosuppressive treatment at the time of vaccination. There are insufficient data to draw conclusions regarding response to other vaccines.

Limited data suggest that Benlysta does not significantly affect the ability to maintain a protective immune response to immunisations received prior to administration of Benlysta. In a substudy, a small group of patients who had previously received either tetanus, pneumococcal or influenza vaccinations were found to maintain protective titres after treatment with Benlysta.

Malignancies and lymphoproliferative disorders

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

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

4.5 Interaction with other medicinal products and other forms of interaction

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

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

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

Pregnancy

There are a limited amount of data from the use of Benlysta in pregnant women. No formal studies have been conducted. Besides an expected pharmacological effect i.e. reduction of B cells, animal studies in monkeys do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). Benlysta should not be used during pregnancy unless the potential benefit justifies the potential risk to the foetus.

Breast-feeding

It is unknown whether Benlysta is excreted in human milk or is absorbed systemically after ingestion. However, belimumab was detected in the milk from female monkeys administered 150 mg/kg every 2 weeks.

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

Fertility

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

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. No detrimental effects on such activities are predicted from the pharmacology of belimumab. The clinical status of the subject and the adverse reaction profile of Benlysta should be borne in mind when considering the patient's ability to perform tasks that require judgement, motor or cognitive skills.

4.8 Undesirable effects

Summary of the safety profile

The safety of belimumab in patients with SLE has been evaluated in 3 pre-registration, placebo-controlled intravenous studies, 1 placebo-controlled subcutaneous study, and one post-marketing, placebo-controlled intravenous study.

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

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

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

Tabulated list of adverse reactions

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

Very common	≥1/10
Common	≥1/100 to <1/10
Uncommon	≥1/1,000 to <1/100
Rare	≥ 1/10,000 to <1/1000

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

System organ class	Frequency	Adverse reaction(s)
Infections and infestations	Very common	Bacterial infections, e.g. bronchitis, urinary tract infection
	Common	Gastroenteritis viral, pharyngitis, nasopharyngitis, viral upper respiratory tract infection
Blood and lymphatic system disorders	Common	Leucopenia
Immune system disorders	Common	Hypersensitivity reactions*
	Uncommon	Anaphylactic reaction
	Rare	Delayed-type, non-acute hypersensitivity reactions
Psychiatric disorders	Common	Depression
	Uncommon	Suicidal behaviour, suicidal ideation
Nervous system disorders	Common	Migraine
Gastrointestinal disorders	Very common	Diarrhoea, nausea
Skin and subcutaneous tissue disorders	Common	Injection site reactions**
	Uncommon	Angioedema, urticaria, rash
Musculoskeletal and connective tissue disorders	Common	Pain in extremity
General disorders and administration site conditions	Common	Infusion or injection -related systemic reactions*, pyrexia

*'Hypersensitivity reactions' covers a group of terms, including anaphylaxis, and can manifest as a range of symptoms including hypotension, angioedema, urticaria or other rash, pruritus, and dyspnoea. 'Infusion or injection -related systemic reactions' covers a group of terms and can manifest as a range of symptoms including bradycardia, myalgia, headache, rash, urticaria, pyrexia, hypotension, hypertension, dizziness, and arthralgia. Due to overlap in signs and symptoms, it is not possible to distinguish between hypersensitivity reactions and infusion reactions in all cases.

**Applies to subcutaneous formulation only.

Description of selected adverse reactions

Data presented below are pooled from the intravenous clinical studies (10 mg/kg intravenous dose only) and the subcutaneous clinical study. Psychiatric disorders also includes data from a post-marketing study.

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

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

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

Psychiatric disorders: In the pre-registration intravenous clinical studies, serious psychiatric events were reported in 1.2% (8/674) of patients receiving Benlysta 10 mg/kg and 0.4% (3/675) of patients receiving placebo. Serious depression was reported in 0.6% (4/674) of patients receiving Benlysta 10 mg/kg and 0.3% (2/675) of patients receiving placebo. There were two suicides in Benlysta-treated patients (including one receiving 1 mg/kg Benlysta).

In a randomised, double-blind, placebo-controlled, post-marketing study with Benlysta 10 mg/kg administered intravenously, serious psychiatric events were reported in 1.0% (20/2002) of patients receiving Benlysta and 0.3% (6/2001) of patients receiving placebo. Serious depression was reported in 0.3% (7/2002) of patients receiving Benlysta and <0.1% (1/2001) of patients receiving placebo. The overall incidence of serious suicidal ideation or behaviour or self-injury without suicidal intent was 0.7% (15/2002) in patients receiving Benlysta and 0.2% (5/2001) in the placebo group. No suicide was reported in either group.

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

In the subcutaneous clinical study, which excluded patients with a history of psychiatric disorders, serious psychiatric events were reported in 0.2% (1/556) of patients receiving Benlysta and in no patients receiving placebo. There were no serious depression-related events or suicides reported in either group.

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

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

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.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
https://sideeffects.health.gov.il/
Additionally, you should also report to GSK Israel (il.safety@gsk.com)

4.9 Overdose

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

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Selective immunosuppressants, ATC code: L04AA26

Mechanism of action

Belimumab is a human IgG1λ monoclonal antibody specific for soluble human B Lymphocyte Stimulator protein (BLyS, also referred to as BAFF and TNFSF13B). Belimumab blocks the binding of soluble BLyS, a B cell survival factor, to its receptors on B cells. Belimumab does not bind B cells directly, but by binding BLyS, belimumab inhibits the survival of B cells, including autoreactive B cells, and reduces the differentiation of B cells into immunoglobulin-producing plasma cells.

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

Pharmacodynamic effects

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

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

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

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

Changes in B cells (including naïve, memory and activated B cells, and plasma cells) and IgG levels occurring in patients during ongoing treatment with intravenous belimumab were followed in a long-term uncontrolled extension study. After 7 and a half years of treatment (including the 72-week parent study), a substantial and sustained decrease in various B cell subsets was observed leading to 87% median reduction in naïve B cells, 67% in memory B cells, 99% in activated B cells, and 92% median reduction in plasma cells after more than 7 years of treatment. After about 7 years, a 28% median reduction in IgG levels was observed, with 1.6% of subjects experiencing a decrease in IgG levels to below 400 mg/dl. Over the course of the study, the reported incidence of AEs generally remained stable or declined.

Immunogenicity

Assay sensitivity for neutralising antibodies and non-specific anti-drug antibody (ADA) is limited by the presence of active drug in the collected samples. The true occurrence of neutralising antibodies and

non-specific anti-drug antibody in the study population is therefore not known. In the two Phase III studies, 4 out of 563 (0.7%) patients in the 10 mg/kg group and 27 out of 559 (4.8%) patients in the 1 mg/kg group tested positive for persistent presence of anti-belimumab antibodies.

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

Clinical efficacy and safety

Intravenous infusion
The efficacy of Benlysta administered intravenously was evaluated in 2 randomized, double-blind, placebo-controlled studies in 1,684 patients with a clinical diagnosis of SLE according to the American College of Rheumatology classification criteria. Patients had active SLE disease, defined as a SELENA-SLEDAI (SELENA=Safety of Estrogens in Systemic Lupus Erythematosus National Assessment; SLEDAI=Systemic Lupus Erythematosus Disease Activity Index) score ≥6 and positive anti-nuclear antibody (ANA) test results (ANA titre ≥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)

* All patients received standard therapy

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

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

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

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

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

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

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

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

Age and race

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

Paediatric population

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

5.2 Pharmacokinetic properties

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

Absorption

Benlysta is administered by intravenous infusion. Maximum serum concentrations of belimumab were generally observed at, or shortly after, the end of the infusion. The maximum serum concentration was 313 µg/ml (range: 173-573 µg/ml) based on simulating the concentration time profile using the typical parameter values of the population pharmacokinetic model.

Distribution

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

Biotransformation

Belimumab is a protein for which the expected metabolic pathway is degradation to small peptides and individual amino acids by widely distributed proteolytic enzymes. Classical biotransformation studies have not been conducted.

Elimination

Serum belimumab concentrations declined in a bi-exponential manner, with a distribution half-life of 1.75 days and terminal half-life 19.4 days. The systemic clearance was 215 ml/day **(**range: 69-622 ml/day).

Special patient populations

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

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

Renal impairment: No specific studies have been conducted to examine the effects of renal impairment on the pharmacokinetics of belimumab. During clinical development Benlysta was studied in patients with SLE and renal impairment (261 subjects with moderate renal impairment, creatinine clearance ≥30 and <60 ml/min; 14 subjects with severe renal impairment, creatinine clearance ≥15 and <30 ml/min). The reduction in systemic clearance estimated by population PK modelling for patients at the midpoints of the renal impairment categories relative to patients with median creatinine clearance in the PK population (79.9 ml/min) were 1.4% for mild (75 ml/min), 11.7% for moderate (45 ml/min) and 24.0% for severe (22.5 ml/min) renal impairment. Although proteinuria (≥ 2 g/day) increased belimumab clearance and

decreases in creatinine clearance decreased belimumab clearance, these effects were within the expected range of variability. Therefore, no dose adjustment is recommended for patients with renal impairment.

Hepatic impairment: No specific studies have been conducted to examine the effects of hepatic impairment on the pharmacokinetics of belimumab. IgG1 molecules such as belimumab are catabolised by widely distributed proteolytic enzymes, which are not restricted to hepatic tissue and changes in hepatic function are unlikely to have any effect on the elimination of belimumab.

Body weight/ Body Mass Index (BMI):

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

Transitioning from intravenous to subcutaneous administration

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

5.3 Preclinical safety data

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

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

Reproductive studies have been performed in pregnant cynomolgus monkeys receiving belimumab 150 mg/kg by intravenous infusion (approximately 9 times the anticipated maximum human clinical exposure) every 2 weeks for up to 21 weeks, and belimumab treatment was not associated with direct or indirect harmful effects with respect to maternal toxicity, developmental toxicity, or teratogenicity.

Treatment-related findings were limited to the expected reversible reduction of B cells in both dams and infants and reversible reduction of IgM in infant monkeys. B cell numbers recovered after the cessation of belimumab treatment by about 1 year post-partum in adult monkeys and by 3 months of life in infant monkeys; IgM levels in infants exposed to belimumab *in utero* recovered by 6 months of age.

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose
Sodium citrate dihydrate
Polysorbate
Citric acid monohydrate

6.2 Incompatibilities

Benlysta is not compatible with 5% glucose.

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

6.3 Shelf life

Unopened vials
The expiry date of the product is indicated on the label and packaging.

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

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

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

6.4 Special precautions for storage

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

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

6.5 Nature and contents of container

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

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

Pack size: 1 vial

6.6 Special precautions for disposal and other handling

Preparation of 120 mg solution for infusion

Reconstitution

Reconstitution and dilution must be carried out under aseptic conditions.

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

It is recommended that a 21-25 gauge needle be used when piercing the vial stopper for reconstitution and dilution. The 120 mg single-use vial of belimumab is reconstituted with 1.5 ml of water for 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.
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Allow the vial to sit at room temperature (15°C to 25°C) during reconstitution, gently swirling the vial for 60 seconds every 5 minutes until the powder is dissolved. Do not shake. Reconstitution is typically complete within 10 to 15 minutes after the water has been added, but it may take up to 30 minutes.

Protect the reconstituted solution from sunlight.

If a mechanical reconstitution device is used to reconstitute Benlysta it should not exceed 500 rpm and the vial should be swirled for no longer than 30 minutes.

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

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

Dilution

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

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

From a 250 ml infusion bag or bottle of sodium chloride 9 mg/ml (0.9%) , sodium chloride 4.5 mg/ml (0.45%), or Lactated Ringer's solution for injection, withdraw and discard a volume equal to the volume of the reconstituted Benlysta solution required for the patient's dose. Then add the required volume of the reconstituted Benlysta solution into the infusion bag or bottle. Gently invert the bag or bottle to mix the solution. Any unused solution in the vials must be discarded.

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

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

Preparation of 400 mg solution for infusion

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

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

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

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

The stream of water for injections should be directed toward the side of the vial to minimize foaming. Gently swirl the vial for 60 seconds.

Allow the vial to sit at room temperature (15°C to 25°C) during reconstitution, gently swirling the vial for 60 seconds every 5 minutes until the powder is dissolved. Do not shake. Reconstitution is typically complete within 10 to 15 minutes after the water has been added, but it may take up to 30 minutes.

Protect the reconstituted solution from sunlight.

If a mechanical reconstitution device is used to reconstitute Benlysta it should not exceed 500 rpm and the vial should be swirled for no longer than 30 minutes.

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

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

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

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

From a 250 ml infusion bag or bottle of sodium chloride 9 mg/ml (0.9%), sodium chloride 4.5 mg/ml (0.45%), or Lactated Ringer's solution for injection, withdraw and discard a volume equal to the volume of the reconstituted Benlysta solution required for the patient's dose. Then add the required volume of the reconstituted Benlysta solution into the infusion bag or bottle. Gently invert the bag or bottle to mix the solution. Any unused solution in the vials must be discarded.

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

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

Method of administration

Benlysta is infused over a 1 hour period.

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

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

Disposal

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

7. MANUFACTURER

Glaxo Group Limited, Brentford, UK.

8. LICENSE HOLDER AND IMPORTER

GlaxoSmithKline (Israel) Ltd., 25 Basel St., Petach Tikva.

9. LICENSE NUMBERS

Benlysta 120 mg	147-37-33499
Benlysta 400 mg	147-38-33510

Ben DR v9