FRONT

GSK

Benlysta
Belimumab

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

QUALITATIVE AND QUANTITATIVE COMPOSITION

Benlysta 120 mg: powder for concentrate for solution for infusion.
Each vial contains 120 mg of belimumab. After reconstitution, the solution contains 80 mg belimumab per mL.

Benlysta 400 mg: powder for concentrate for solution for infusion.
Each vial contains 400 mg of belimumab. After reconstitution, the solution contains 80 mg belimumab per mL.

Belimumab is a human IgG1λ monoclonal antibody produced in a mammalian cell line (NS0) by recombinant DNA technology. For the full list of excipients, see section List of excipients.

PHARMACEUTICAL FORM

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

CLINICAL PARTICULARS

Therapeutic indications

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

Benlysta is indicated in combination with background immunosuppressive therapies for the treatment of adult patients with active lupus nephritis (see sections Posology and method of administration and Pharmacodynamic properties).

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 Special warnings and precautions for use and Undesirable effects). 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 Posology and method of administration).

Posology

Premedication including an antihistamine, with or without an antipyretic, may be administered before the infusion of Benlysta (see section Special warnings and precautions for use).

In paediatric patients 5 years of age and older (see section Pharmacodynamic properties), Benlysta should be used with caution in the absence of data on efficacy in patients with severe active lupus nephritis. 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.

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

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

Switch from intravenous to subcutaneous administration

SLE

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

Lupus nephritis

If patients with lupus nephritis is being transitioned from Benlysta intravenous administration to subcutaneous administration, the first dose of 200 mg subcutaneous injection should be administered 1 to 2 weeks after the last intravenous dose. The intervals should occur any time after the patient completes the first 2 intravenous doses (see section Pharmacokinetic properties).

Special populations

Elderly

Data on patients aged 65 years and older (see section Pharmacodynamic properties), Benlysta should be used with caution in the elderly. Dose adjustment is not required (see section Pharmacokinetic properties).

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 Pharmacokinetic properties).

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 Pharmacokinetic properties).

Paediatric population

SLE

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

The safety and efficacy of Benlysta in children aged between 5 years have not been established. No data are available.

Lupus nephritis

The safety and efficacy of Benlysta in children and adolescents aged below 18 years with severe active lupus nephritis have not been established. No data are available.

Method of administration

Benlysta is administered intravenously by infusion, and must be reconstituted and diluted before administration. For instructions on reconstitution, dilution, and storage of the medicinal product before administration, see section Special precautions for disposal and other handling.

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 Special warnings and precautions for use and Undesirable effects).

Contraindications

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

Special warnings and precautions for use

Traceability

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

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

- severe active central nervous system lupus (see section Pharmacodynamic properties)
- HIV
- a history of, or current, hepatitis B or C
- hypogammaglobulinemia (IgG <400 mg/dL), IgA deficiency (IgA <20 mg/dL)
- a history of major organ transplant or hematopoietic stem cell/marrow transplant or renal transplant.

Concomitant use with B-cell targeted therapy

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

Infusion reactions and hypersensitivity

Administration of Benlysta may result in hypersensitivity reactions and infusion reactions which can be severe, and fatal, in the event of a severe reaction, Benlysta administration must be interrupted and appropriate medical therapy administered (see section Posology and method of administration). 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 0.3% of adult patients, and included anaphylactic reaction, bradycardia, hypotension, angioedema, and dyspnoea. Infusion reactions occurred more frequently during the first two infusions and tended to decrease with subsequent infusions (see section Undesirable effects). 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 Posology and method of administration and Undesirable effects). 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 Posology and method of administration).

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

Infections

The mechanism of action of belimumab could increase the risk for the development of infections in adults and children with lupus, including opportunistic infections, and younger children may be at higher risk. In controlled clinical studies, the incidence of serious infections was similar across the Benlysta and placebo groups; however, fatal infections (e.g., pneumonia and sepsis) occurred more frequently in patients receiving Benlysta compared with placebo (see section Undesirable effects). Pneumonia, sepsis and viral infections were the most frequent fatal infections. Before initiating treatment, Benlysta should be initiated in patients with active serious infections (including serious chronic infections). Physicians should exercise caution and carefully assess if the benefits are expected to outweigh the risks when considering the use of Benlysta in patients with a history of recurrent infections. Physicians should advise patients to contact their health care provider if they develop symptoms of an infection. Patients who develop an infection while undergoing treatment with Benlysta should be monitored closely and careful consideration given to interrupting immunosuppressant therapy including Benlysta until the infection is resolved. The risk of using Benlysta in patients with active or latent tuberculosis is unknown.

Depression and suicidality

In controlled clinical intravenous and subcutaneous studies, psychiatric disorders (depression, suicidal ideation and behaviour including suicide) have been reported more frequently in patients receiving Benlysta (see section Undesirable effects). 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 as clinically indicated. If PML is suspected, immunosuppressant therapy including Benlysta, must be suspended until PML has been excluded. If PML is confirmed, immunosuppressant therapy, including Benlysta, must be discontinued.

Immunization

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 immunizations. 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 immunizations recommended prior to administration of Benlysta. In a subsidiary, 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.

Malignancy 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'.

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 enzymes. 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, or administered dose is individually adjusted (e.g. warfarin).

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 limited amount of data from the use of Benlysta in pregnant women. No formal studies have been conducted. Belimumab expected pharmacological effect, i.e. reduction of B cells, animal studies in monkeys do not indicate direct or indirect harmful effects with respect to reproduction toxicity (see section Preclinical safety data).

Benlysta should not be used during pregnancy unless the potential benefit justifies the potential risk to the foetus.

Breastfeeding

It is unknown whether Benlysta is excreted in human milk or is absorbed systemically after ingestion. However, belimumab was detected in the milk of cynomolgus monkeys (see section Preclinical safety data).

Because maternal antibodies (IgG) are excreted in breast milk, it is recommended that a decision should be made whether to discontinue breastfeeding or to discontinue Benlysta therapy, taking into account the benefit of breastfeeding 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 Preclinical safety data).

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 pharmacological effect or profile of the medicinal product. 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.

Undesirable effects

Summary of the safety profile in adults

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

The data presented in the table below reflect exposure in 674 patients from the three pre-registration clinical studies and 370 patients in the subsequent placebo-controlled study with SLE administered Benlysta intravenously (10 mg/kg over a 1-hour period) on Days 0, 14, 28, and then every 28 days for up to 52 weeks, and 556 patients with SLE exposed to Benlysta subcutaneously (200 mg once weekly) up to 52 weeks. The safety data presented include data beyond Week 52 in some patients with SLE. The data reflect additional exposure in 224 patients with active lupus nephritis who received Benlysta intravenously (10 mg/kg for up to 104 weeks). Data from post-marketing reports are also included.

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

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

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

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 <1/1,000
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	Common	Diarrhoea, nausea
Skin and subcutaneous tissue disorders	Common	Injection site reactions‡, urticaria, rash
	Uncommon	Angioedema
Musculoskeletal and connective tissue disorders	Common	Pain in extremity
General disorders and administration site conditions	Common	Infusion or injection-related systemic reactions§, pyrexia

* See "Description of selected adverse reactions" and section Special warnings and precautions for use "Infections" for further information.
† 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 hypotension, myalgia, headache, rash, pruritus, dyspnea, hypotension, hypertension, dizziness, and arrhythmia. Due to overlap in signs and symptoms, it is not possible to distinguish between hypersensitivity reactions and infusion or injection-related systemic reactions in all cases.
‡ Applies to subcutaneous formulation only.

Description of selected adverse reactions

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

Infusion or injection-related systemic reactions and hypersensitivity: Infusion or injection-related systemic reactions and hypersensitivity were generally observed on the day of administration, but acute hypersensitivity reactions may also occur several days after dosing. Patients with a history of multiple drug allergies or significant hypersensitivity reactions may be at increased risk. The incidence of infusion reactions and hypersensitivity reactions after intravenous administration occurring within 3 days of an infusion was 12% in the group receiving Benlysta and 10% in the group receiving placebo, with 1.2% and 0.2%, respectively, requiring permanent treatment discontinuation.

Infections: The overall incidence of infections in intravenous and subcutaneous pre-registration SLE studies was 62% 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: 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 events, 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 serious or fatal.

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

In the lupus nephritis study, patients were receiving a background of standard therapy (see section Pharmacodynamic properties) and the overall incidence of infections was 82% in patients receiving Benlysta compared with 76% in patients receiving placebo. Serious infections occurred in 13.8% of patients receiving Benlysta and in 7.14% of patients receiving placebo. Fatal infections occurred in 0.9% (2/224) of patients receiving Benlysta and in 0.9% (2/224) of patients receiving placebo.

In a randomized, double-blind, 52-week, post-marketing safety SLE study (BLISS-52x07) which assessed mortality and specific adverse events, in adults, serious infections occurred in 12.9% of patients receiving Belimumab (10 mg/kg intravenously), 12.1% of patients receiving placebo, however, fatal infections (e.g., pneumonia and sepsis) occurred in 0.6% (9/2002) of Belimumab-treated patients vs 0.15% (1/2001) of patients receiving placebo, while the incidence of all-cause mortality was 0.50% (10/2002) vs 0.4% (8/2001), respectively. Most fatal infections were observed during the first 20 weeks of treatment with Benlysta.

Psychiatric disorders: In the pre-registration intravenous SLE clinical studies, serious psychiatric events were reported in 1.2% (8/674) of patients receiving Benlysta 10 mg/kg and 0.4% (3/674) 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 post-marketing SLE study, serious psychiatric events were reported in 1.29% (12/930) of patients receiving Benlysta and 0.1% (1/2001) of patients receiving placebo. Serious depression was reported in 0.3% (3/930) of patients receiving Benlysta and 0.5% (10/2001) of patients receiving placebo. There were no suicides in Belimumab-treated patients (including one receiving 1 mg/kg Belimumab).

In a post-marketing SLE study, serious psychiatric events were reported in 1.29% (12/930) of patients receiving Benlysta and 0.1% (1/2001) of patients receiving placebo. Serious depression was reported in 0.3% (3/930) of patients receiving Benlysta and 0.5% (10/2001) of patients receiving placebo. The overall incidence of serious suicidal ideation or behaviour without suicide attempt was 0.7% (13/2002) in patients receiving Belimumab and 0.2% (5/2001) in the placebo group. No suicide was reported in either group.

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

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

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

Leukoencephalitis: Chronic graft versus host disease (GVHD) in patients receiving Benlysta, and in patients receiving Belimumab expected pharmacological effect i.e. reduction of B cells, animal studies in monkeys do not indicate direct or indirect harmful effects with respect to reproduction toxicity (see section Preclinical Safety data).

Benlysta should not be used during pregnancy unless the potential benefit justifies the potential risk to the foetus.

Breastfeeding

It is unknown whether Benlysta is excreted in human milk or is absorbed systemically after ingestion. However, belimumab was detected in the milk of cynomolgus monkeys (see section Preclinical safety data).

Because maternal antibodies (IgG) are excreted in breast milk, it is recommended that a decision should be made whether to discontinue breastfeeding or to discontinue Benlysta therapy, taking into account the benefit of breastfeeding 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 Preclinical safety data).

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 pharmacological effect or profile of the medicinal product. 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.

Undesirable effects

Summary of the safety profile in adults

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

The data presented in the table below reflect exposure in 674 patients from the three pre-registration clinical studies and 370 patients in the subsequent placebo-controlled study with SLE administered Benlysta intravenously (10 mg/kg over a 1-hour period) on Days 0, 14, 28, and then every 28 days for up to 52 weeks, and 556 patients with SLE exposed to Benlysta subcutaneously (200 mg once weekly) up to 52 weeks. The safety data presented include data beyond Week 52 in some patients with SLE. The data reflect additional exposure in 224 patients with active lupus nephritis who received Benlysta intravenously (10 mg/kg for up to 104 weeks). Data from post-marketing reports are also included.

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

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

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Tabulated list of adverse reactions

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

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Uncommon ≥1/1,000 to <1/100
Rare ≥1/10,000 to <1/1,000
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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

Version: 3 Artwork Information Panel (AIP)
Manufacturing Site Number: 62000000091815
Manufacturing Site(s): GSK_PARMA_ITALY
Technical Drawing (Do NOT include version number): D150311LEA
Product Market Trade Name: Benlysta
Approving Market(s): MARKET GROUP-Gulf and Near East
Material Spec: (Do NOT include version number): N/A
Print Process: N/A
Colour Standard Reference: N/A
Material Type: N/A
Total Colours & Varnishes: 1
BLACK
Total Special Finishes: 0
Body Size: 7.0pt
Smallest Text Size: 7.0pt
Leading: 7.3pt
Horizontal Scale: 85%
Additional Info (1): N/A
Additional Info (2): N/A
Microtext: N
Additional Info (3): N/A
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200 mm Measuring Bar

BACK

Benlysta
Belimumab

NOTE TO MARKET

Local approvers must ensure that trade mark and copyright statements included in the brief comply with guidelines provided by Legal: Global Trade Marks.

IMPORTANT

GSK LOC is responsible to approve the change documentation, artwork brief and final artwork, ensuring that it is accurate, consistent and complete.

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GSK Market is responsible to advise SDC when changes required impact the following:

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BACK

Table 4 – Paediatric response rate at Week 52

Response*	Placebo (n=40)	Benlysta 10 mg/kg (n=53)
SLE Responder Index (%)	43.4 (17/39)	57.8 (30/53)
Odds ratio (95% CI) vs placebo		1.49 (0.64, 3.46)
Components of SLE Responder Index		
Percent of patients with reduction in SELENA-SLEDAI ≥4 (%)	41.6 (17/39)	54.7 (29/53)
Odds ratio (95% CI) vs placebo		1.62 (0.69, 3.78)
Percent of patients with no worsening by BILAG index (%)	61.5 (24/39)	75.6 (39/53)
Odds ratio (95% CI) vs placebo		1.96 (0.77, 4.97)
Percent of patients with no worsening by PGA (%)	66.7 (26/39)	75.5 (40/53)
Odds ratio (95% CI) vs placebo		1.70 (0.66, 4.38)

*Analyses included any subject missing a baseline assessment for any of the components (1 for placebo).
Among patients experiencing a severe flare, the median study day of the first severe flare was Day 150 in the Benlysta group and Day 113 in the placebo group. Severe flares were observed in 17.0% of the Benlysta group compared to 35.0% of the placebo group over 1 to 52 weeks of observation (Odd ratio [Odds ratio] 0.38, [95% CI: 0.15, 0.96]). This was consistent with the findings from the adult intravenous clinical trials.

Using the Paediatric Rheumatology International Trials Organisation/American College of Rheumatology (PRINTO/ACR) Juvenile SLE Response Evaluation Criteria, a higher proportion of paediatric patients receiving Benlysta demonstrated improvement compared with placebo (Table 5).

Table 5 – PRINTO/ACR response rate at Week 52

	Proportion of patients with at least 50% improvement in any 2 of 5 components* and no more than one of the remaining worsening by more than 30%		Proportion of patients with at least 30% improvement in 3 of 5 components* and no more than one of the remaining worsening more than 30%	
	Placebo (n=40)	Benlysta 10 mg/kg (n=53)	Placebo (n=40)	Benlysta 10 mg/kg (n=53)
Response, n (%)	14/40 (35.0)	32/53 (60.4)	17/40 (42.5)	38/53 (71.8)
Observed difference vs Placebo		25.38		29.33
Odds ratio (95% CI) vs Placebo		2.74 (1.15, 6.54)		3.92 (1.79, 7.77)

*The five PRINTO/ACR components were percent change at Week 52 in: Patient's Global Assessment, Physical Exam, PGA, SELENA-SLEDAI scores, 24-hour proteinuria, and, Paediatric Quality of Life Inventory™ Generic Core Scale (PedsQL GCS) physical functioning domain score.

Pharmacokinetic properties

The intravenous pharmacokinetic parameters quoted below are based on population parameter estimates for the 563 patients with SLE who received Benlysta 1 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 mean 313 µg/mL (range: 17.5–731 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 day and terminal half-life 19.4 day. The apparent clearance was 215 mL/day (range: 69-622 mL/day).

Lupus nephritis study

A population pharmacokinetic analysis was conducted in 224 adult patients with lupus nephritis who received Benlysta 10 mg/kg intravenously (Days 0, 14, 28, and then every 28 days up to 104 weeks). In patients with lupus nephritis, active renal disease activity, belimumab clearance was initially higher than observed in SLE studies; however, after 24 weeks of treatment and throughout the remainder of the study, belimumab clearance and exposure were similar to that observed in adult patients with SLE who received Benlysta 10 mg/kg intravenously.

Special patient populations

Paediatric population: The pharmacokinetic parameters are based on individual parameter estimates from a population pharmacokinetic analysis of 53 patients from a study in paediatric patients with SLE. Following intravenous administration of 10 mg/kg on Day 0, 14 and 28, and at 4-week intervals thereafter, belimumab exposures were similar between paediatric and adult SLE subjects. Steady-state geometric mean Cmax, Cmin, and AUC values were 306 µg/mL, 42 µg/mL, and 2369 day•µg/mL in the 12 to <18 year-olds (n=32), and 317 µg/mL, 52 µg/mL, and 3126 day•µg/mL in the 4 to <12 year-olds (n=21), respectively.

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 trials patient Benlysta was staged in patients with SLE and renal impairment (24 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 system clearance estimated by population PK modelling for patients in the subjects 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), 17% for moderate (35 mL/min) and 24.2% for severe (22.5 mL/min) renal impairment. Although proteinuria did global 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 catabolized 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-normalized belimumab dosing leads to decreased exposure for underweight subjects (BMI <18.5) and to increased exposure for obese subjects (BMI ≥35). 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 with SLE 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 Posology and method of administration). Based on simulations with population PK parameters, the steady-state average belimumab concentrations for 200 mg subcutaneous weekly administration were similar to 10 mg/kg intravenous every 4 weeks.

Lupus nephritis

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

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 16 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 postpartum 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 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.

PHARMACEUTICAL PARTICULARS

List of excipients

Citric acid monohydrate
Sodium citrate dihydrate
Sucrose
Polysorbate 80

Incompatibilities

Benlysta is not compatible with 5% glucose.
This medicinal product must not be mixed with other medicinal products except those mentioned in section Special precautions for disposal and other handling

Shelf life

Unopened vial:
The expiry date is indicated on the 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 containing diluted belimumab 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 at room temperature.

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

Special precautions for storage

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 Shelf life

Nature and contents of container

Benlysta 120 mg powder for concentrate for solution for infusion

Type I glass vial (10 mL), sealed with a bromobutyl rubber stopper and a flip-off aluminium seal containing 120 mg of powder.
Pack size: 1 vial

Benlysta 400 mg powder for concentrate for solution for infusion

Type I glass vial (20 mL), sealed with a bromobutyl rubber stopper and a flip-off aluminium seal containing 400 mg of powder.
Pack size: 1 vial

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.

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 minimise foaming. Gently swirl the vial for 60 seconds. Allow the vial to sit at room temperature (up to 15 minutes) and gently swirl 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 vial should be swirled for no longer than 30 minutes.

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

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. For patients whose body weight is less than or equal to 40 kg, infusion bags with 100 mL of these diluents may be considered providing that the resulting belimumab concentration in the infusion bag does not exceed 4 mg/mL.

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

From a 250 mL (or 100 mL) infusion bag or bottle of sodium chloride 9 mg/mL (0.9%), sodium chloride 4.5 mg/mL (0.45%), or Lactated Ringer's solution for 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 vial 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.

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 minimise foaming. Gently swirl the vial for 60 seconds. Allow the vial to sit at room temperature during reconstitution, gently swirling the vial for 60 seconds every 5 minutes until the powder is dissolved. Do not shake. Reconstitution is typically complete within 10 to 15 minutes after the 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 vial should be swirled for no longer than 30 minutes.

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

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 vial 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 polyethylene bags have been observed.

Disposal

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

Manufactured and Packed by:
GlaxoSmithKline Manufacturing S.p.A., Parma, Italy.

Marketing Authorisation Holder:
GlaxoSmithKline UK Limited, 980 Great West Road, Brentford, Middlesex, United Kingdom

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THIS IS A MEDICAMENT

- Medicament is a product which affects your health and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are the experts in medicines, their benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed.
- Do not repeat the same prescription without consulting your doctor.
- Keep all medicaments out of the reach of children.

Council of Arab Health Ministers,
Union of Arab Pharmacists

620000000091815

Version: 3	Artwork Information Panel (AIP)		GSK
Manufacturing Site Number: 620000000091815	Manufacturing Site(s): GSK_PARMA_ITALY	Technical Drawing (Do NOT include version number): D15031LEA	
Product Market Trade Name: Benlysta	Approving Market(s): MARKET GROUP-Gulf and Near East	Material Spec: (Do NOT include version number): N/A	
Print Process: N/A	Colour Standard Reference: N/A	Material Type: N/A	N/A
Total Colours & Varnishes: 1		Body Text Size: 7.0pt	Smallest Text Size: 7.0pt
BLACK		Leading: 7.3pt	
Total Special Finishes: 0		Horizontal Scale: 85%	
		Microtext: N	
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200 mm Measuring Bar

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IMPORTANT

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Formulation, Tablet embossing, Storage conditions and Shelf Life