Certificate Number: PP10191843

SUMMARY OF PRODUCT CHARACTERISTICS

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

1 NAME OF THE MEDICINAL PRODUCT

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

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Pre-filled pen

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

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

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection in pre-filled pen (injection)

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

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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

4.2 Posology and method of administration

Benlysta treatment should be initiated and supervised by a qualified physician experienced in the diagnosis and treatment of SLE. It is recommended that the first subcutaneous injection of Benlysta should be under the supervision of a healthcare professional in a setting that is sufficiently qualified to manage hypersensitivity reactions, if necessary. The healthcare professional must provide proper training in subcutaneous technique and education about signs and symptoms of hypersensitivity reactions (see

section 4.4). A patient may self-inject, or the patient caregiver may administer Benlysta after the healthcare professional determines that it is appropriate.

Posology

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

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

Missed doses

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

Changing the weekly dosing day

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

Transition from intravenous to subcutaneous administration

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 5.2).

Lupus nephritis
If a patient 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. This transition should occur any time after the patient completes the first 2 intravenous doses (see section 5.2).

Special populations

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

SUMMARY OF PRODUCT CHARACTERISTICS

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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 subcutaneous administration in children and adolescents (< 18 years of age) have not been established. No data are available.

Method of administration

The pre-filled pen or pre-filled syringe should be used for subcutaneous injection only. The recommended injection sites are the abdomen or thigh. When injecting in the same region, patients should be advised to use a different injection site for each injection; injections should never be given into areas where the skin is tender, bruised, red, or hard. When a 400 mg dose is administered at the same site, it is recommended that the 2 individual 200 mg injections are administered at least 5 cm (approximately 2 inches) apart.

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

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Traceability

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

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

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

SUMMARY OF PRODUCT CHARACTERISTICS

Printed for Certificate of Pharmaceutical Product

Concomitant use with B cell targeted therapy

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

Hypersensitivity

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

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

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

Infections

The mechanism of action of belimumab could increase the risk for the development of infections, including opportunistic infections. In controlled clinical studies, the incidence of serious infections was similar across the Benlysta and placebo groups; however, fatal infections (e.g. pneumonia and sepsis) occurred more frequently in patients receiving Benlysta compared with placebo (see section 4.8). Pneumococcal vaccination should be considered before initiating Benlysta treatment. Benlysta should not 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 infection. 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 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 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 belimumab, must be discontinued.

Immunisation

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

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

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

Malignancies and lymphoproliferative disorders

Immunomodulatory medicinal products, including Benlysta, may increase the risk of malignancy. Caution 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 three pre-registration placebo-controlled intravenous studies and one subsequent regional placebo-controlled intravenous study, one

placebo-controlled subcutaneous study, and two post-marketing placebo-controlled intravenous studies; the safety in patients with active lupus nephritis has been evaluated in one placebo-controlled intravenous study.

The data presented in the table below reflect exposure in 674 patients with SLE from the three pre-registration clinical studies and 470 patients in the subsequent placebo-controlled study administered Benlysta intravenously (10 mg/kg 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, immunomodulatory medicinal products, anti-malarials, non-steroidal anti-inflammatory medicinal products.

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

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

Tabulated list of adverse reactions

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

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

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

SUMMARY OF PRODUCT CHARACTERISTICS

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System organ class	Frequency	Adverse reaction(s)
Infections and infestations[1]	Very common	Bacterial infections, e.g. bronchitis, urinary tract infection
	Common	Gastroenteritis viral, pharyngitis, nasopharyngitis, viral upper respiratory tract infection
Blood and lymphatic system disorders	Common	Leucopenia
Immune system disorders	Common	Hypersensitivity reactions[2]
	Uncommon	Anaphylactic reaction
	Rare	Delayed-type, non-acute hypersensitivity reactions
Psychiatric disorders	Common	Depression
	Uncommon	Suicidal behaviour, suicidal ideation
Nervous system disorders	Common	Migraine
Gastrointestinal disorders	Common	Diarrhoea, nausea
Skin and subcutaneous tissue disorders	Common	Injection site reactions[3] , urticaria, rash
	Uncommon	Angioedema
Musculoskeletal and connective tissue disorders	Common	Pain in extremity
General disorders and administration site conditions	Common	Infusion or injection-related systemic reactions[2], pyrexia

[1] See 'Description of selected adverse reactions' and section 4.4 'Infections' for further information.
[2] 'Hypersensitivity reactions' covers a group of terms, including anaphylaxis, and can manifest as a range of symptoms including hypotension, angioedema, urticaria or other rash, pruritus, and dyspnoea. 'Infusion or injection-related systemic reactions' covers a group of terms and can manifest as a range of symptoms including bradycardia, myalgia, headache, rash, urticaria, pyrexia, hypotension, hypertension, dizziness, and arthralgia. Due to overlap in signs and symptoms, it is not possible to distinguish between hypersensitivity reactions and infusion or injection-related systemic reactions in all cases.
[3] Applies to subcutaneous formulation only.

SUMMARY OF PRODUCT CHARACTERISTICS

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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 0.3 %, respectively, requiring permanent treatment discontinuation.

The incidence of post-injection systemic reactions and hypersensitivity reactions occurring within 3 days of subcutaneous administration was 7 % in the group receiving Benlysta and 9 % in the group receiving placebo. Clinically significant hypersensitivity reactions associated with Benlysta administered subcutaneously and requiring permanent treatment discontinuation were reported in 0.2 % of patients receiving Benlysta and in no patients receiving placebo.

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

In the lupus nephritis study, patients were receiving a background of standard therapy (see section 5.1) and the overall incidence of infections was 82 % in patients receiving Benlysta compared with 76 % in patients receiving placebo. Serious infections occurred in 13.8 % of patients receiving Benlysta and in 17.0 % of patients receiving placebo. Fatal infections occurred in 0.9 % (2/224) of patients receiving Benlysta and in 0.9 % (2/224) of patients receiving placebo.

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

Psychiatric disorders: In the pre-registration intravenous SLE clinical studies, serious psychiatric events were reported in 1.2 % (8/674) of patients receiving Benlysta 10 mg/kg 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).

SUMMARY OF PRODUCT CHARACTERISTICS

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

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

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

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

Injection site reactions: In the subcutaneous SLE study, the frequency of injection site reactions was 6.1 % (34/556) and 2.5 % (7/280) for patients receiving Benlysta and placebo, respectively. These injection site reactions (most commonly pain, erythema, hematoma, pruritus and induration) were mild to moderate in severity. The majority did not necessitate drug discontinuation.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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: Immunosuppressants, monoclonal antibodies, ATC code: L04AG04

SUMMARY OF PRODUCT CHARACTERISTICS

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Mechanism of action

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

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

Pharmacodynamic effects

Median IgG levels at Week 52 were reduced by 11 % in patients with SLE receiving Benlysta compared with an increase of 0.7 % in patients receiving placebo.

In patients with anti-dsDNA antibodies at baseline, median anti-dsDNA antibodies levels at Week 52 were reduced by 56 % in patients receiving Benlysta compared with 41 % in patients receiving placebo. In patients with anti-dsDNA antibodies at baseline, by Week 52, 18 % of patients treated with Benlysta had converted to anti-dsDNA negative compared with 15 % of the patients receiving placebo.

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

Benlysta significantly reduced circulating overall, transitional, naïve, and SLE B cells, as well as plasma cells at Week 52. Reductions in naïve and transitional B cells, as well as the SLE B cell subset were observed as early as Week 8. Memory cells increased initially and slowly declined toward baseline levels by Week 52.

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

In patients with active lupus nephritis, following treatment with Benlysta (10 mg/kg intravenously) or placebo, there was an increase in serum IgG levels which was associated with decreased proteinuria. Relative to placebo, smaller increases in serum IgG levels were observed in the Benlysta group as expected with the known mechanism of belimumab. At Week 104, the median percent increase from baseline in IgG was 17 % for Benlysta and 37 % for placebo. Reductions in autoantibodies, increases in complement, and reductions in circulating total B cells and B-cell subsets observed were consistent with the SLE studies.

SUMMARY OF PRODUCT CHARACTERISTICS

Printed for Certificate of Pharmaceutical Product

Immunogenicity

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

Clinical efficacy and safety

SLE

Subcutaneous injection
The efficacy of Benlysta administered subcutaneously was evaluated in a randomised, double-blind, placebo-controlled 52-week Phase III study (HGS1006-C1115; BEL112341) in 836 adult patients with a clinical diagnosis of SLE according to the American College of Rheumatology classification criteria. Eligible patients had active SLE disease, defined as a SELENA-SLEDAI score ≥ 8 and positive anti-nuclear antibody (ANA or anti-dsDNA) test results (ANA titre ≥ 1:80 and/or a positive anti-dsDNA [≥ 30 units/mL]) at screening. Patients were on a stable SLE treatment regimen (standard of care) consisting of any of the following (alone or in combination): corticosteroids, anti-malarials, NSAIDs or other immunosuppressives. Patients were excluded from the study if they had severe active central nervous system lupus or severe active lupus nephritis.

This study was conducted in the US, South America, Europe and Asia. Patient median age was 37 years (range: 18 to 77 years), and the majority (94 %) were female. Background medicinal products included corticosteroids (86 %; > 7.5 mg/day prednisone equivalent 60 %), immunosuppressives (46 %), and anti-malarials (69 %). Patients were randomised in a 2:1 ratio to receive belimumab 200 mg or placebo subcutaneously once weekly for 52 weeks.

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

The primary efficacy endpoint was a composite endpoint (SLE Responder Index) that defined response as meeting each of the following criteria at Week 52 compared with baseline:

- ≥ 4-point reduction in the SELENA-SLEDAI score, and
- no new British Isles Lupus Assessment Group (BILAG) A organ domain score or 2 new BILAG B organ domain scores, and
- no worsening (< 0.30 point increase) in Physician's Global Assessment score (PGA)

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

SUMMARY OF PRODUCT CHARACTERISTICS

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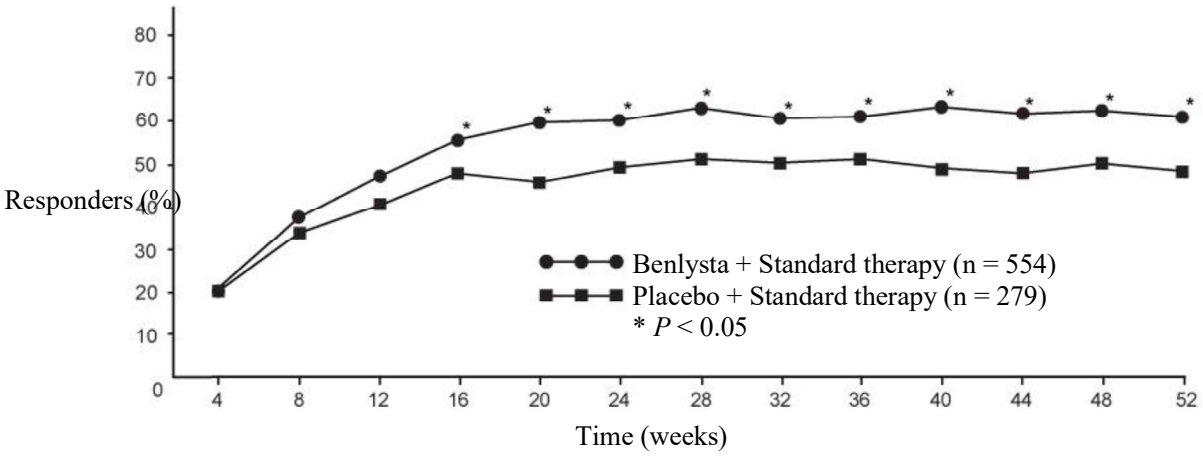
Table 1. Response rate at Week 52

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

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

The differences between the treatment groups were apparent by Week 16 and sustained through Week 52 (Figure 1).

Figure 1. Proportion of SRI responders by visit



SUMMARY OF PRODUCT CHARACTERISTICS

Printed for Certificate of Pharmaceutical Product

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

The percentage of patients receiving greater than 7.5 mg/day prednisone (or equivalent) at baseline whose average corticosteroid dose was reduced by at least 25 % from baseline to a dose equivalent to prednisone ≤ 7.5 mg/day during Weeks 40 through 52, was 18.2 % in the group receiving Benlysta and 11.9 % in the group receiving placebo (p = 0.0732).

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

Subgroup analysis of the primary endpoint demonstrated that the greatest benefit was observed in patients with higher disease activity at baseline including patients with SELENA SLEDAI scores ≥ 10 or patients requiring steroids to control their disease or patients with low complement levels.

An additional, previously identified serologically active group, those patients with low complement and positive anti-dsDNA at baseline, also demonstrated a greater relative response, see Table 2 for results of this example of a higher disease activity group.

SUMMARY OF PRODUCT CHARACTERISTICS

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

Subgroup	Anti-dsDNA positive AND low complement	
	Placebo	**Benlysta 200 mg weekly**
	(n = 108)	(n = 246)
SRI response rate at Week 52[1] (%)	47.2	64.6 (p = 0.0014)
Observed treatment difference vs. placebo (%)		17.41
Severe flares over 52 weeks:	(n = 108)	(n = 248)
Patients experiencing a severe flare (%)	31.5	14.1
Observed treatment difference vs. placebo (%)		17.4
Time to severe flare [Hazard ratio (95 % CI)]		0.38 (0.24, 0.61) (p < 0.0001)
	(n = 70)	(n = 164)
Prednisone reduction by ≥ 25 % from baseline to ≤ 7.5 mg/day during weeks 24 through 52[2] (%)	11.4	20.7 (p = 0.0844)
Observed treatment difference vs. placebo (%)		9.3
	(n = 108)	(n = 248)
FACIT-fatigue score improvement from baseline at Week 52 (mean):	2.4	4.6 (p = 0.0324)
Observed treatment difference vs. placebo (median difference)		2.1

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

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

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

SUMMARY OF PRODUCT CHARACTERISTICS

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Lupus nephritis

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

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

Intravenous infusion
The efficacy and safety of Benlysta 10 mg/kg administered intravenously over a 1-hour period on Days 0, 14, 28, and then every 28 days, were evaluated in a 104-week randomised (1:1), double-blind, placebo-controlled, Phase III study (BEL114054) in 448 patients with active lupus nephritis. The patients had a clinical diagnosis of SLE according to ACR classification criteria, biopsy proven lupus nephritis Class III, IV, and/or V and had active renal disease at screening requiring standard therapy. Standard therapy included corticosteroids, 0 to 3 intravenous administrations of methylprednisolone (500 to1000 mg per administration), followed by oral prednisone 0.5 to1 mg/kg/day with a total daily dose ≤60 mg/day and tapered to ≤ 10 mg/day by Week 24, with:

- mycophenolate mofetil 1 to 3 g/day orally or mycophenolate sodium 720 to 2160 mg/day orally for induction and maintenance, or
- cyclophosphamide 500 mg intravenously every 2 weeks for 6 infusions for induction followed by azathioprine orally at a target dose of 2 mg/kg/day for maintenance.

This study was conducted in Asia, North America, South America, and Europe. Patient median age was 31 years (range: 18 to 77 years); the majority (88 %) were female.

The primary efficacy endpoint was Primary Efficacy Renal Response (PERR) at Week 104 defined as a response at Week 100 confirmed by a repeat measurement at Week 104 of the following parameters: urinary protein:creatinine ratio (uPCR) ≤ 700 mg/g (79.5 mg/mmol) and estimated glomerular filtration rate (eGFR) ≥ 60 mL/min/1.73 m^2 or no decrease in eGFR of > 20 % from pre-flare value.

The major secondary endpoints included:

- Complete Renal Response (CRR) defined as a response at Week 100 confirmed by a repeat measurement at Week 104 of the following parameters: uPCR < 500 mg/g (56.8 mg/mmol) and eGFR ≥ 90 mL/min/1.73 m^2 or no decrease in eGFR of > 10 % from pre-flare value.
- PERR at Week 52.
- Time to renal-related event or death (renal-related event defined as first event of end-stage renal disease, doubling of serum creatinine, renal worsening [defined as increased proteinuria, and/or impaired renal function], or receipt of renal disease-related prohibited therapy).

For PERR and CRR endpoints, steroid treatment had to be reduced to ≤ 10 mg/day from Week 24 to be considered a responder. For these endpoints, patients who discontinued treatment early, received prohibited medication, or withdrew from the study early were considered non-responders.

The proportion of patients achieving PERR at Week 104 was significantly higher in patients receiving Benlysta compared with placebo. The major secondary endpoints also showed significant improvement with Benlysta compared with placebo (Table 3).

SUMMARY OF PRODUCT CHARACTERISTICS

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Table 3. Efficacy results in adult patients with lupus nephritis

Efficacy endpoint	**Placebo** **(n = 223)**	**Benlysta 10 mg/kg** **(n = 223)**	**Observed difference vs. placebo**	**Odds/Hazard ratio vs. placebo (95 % CI)**	**P-value**
PERR at Week 104[1] Responders	32.3 %	43.0 %	10.8 %	OR 1.55 (1.04, 2.32)	0.0311
Components of PERR					
Urine protein:creatinine ratio ≤ 700 mg/g (79.5 mg/mmol)	33.6 %	44.4 %	10.8 %	OR 1.54 (1.04, 2.29)	0.0320
eGFR≥ 60 mL/min/1.73 m^2 or no decrease in eGFR from pre-flare value of > 20 %	50.2 %	57.4 %	7.2 %	OR 1.32 (0.90, 1.94)	0.1599
Not treatment failure[3]	74.4 %	83.0 %	8.5 %	OR 1.65 (1.03, 2.63)	0.0364
CRR at Week 104[1] Responders	19.7 %	30.0 %	10.3 %	OR 1.74 (1.11, 2.74)	0.0167
Components of CRR					
Urine protein:creatinine ratio < 500 mg/g (56.8 mg/mmol)	28.7 %	39.5 %	10.8 %	OR 1.58 (1.05, 2.38)	0.0268
eGFR≥ 90 mL/min/1.73 m^2 or no decrease in eGFR from pre-flare value of > 10 %	39.9 %	46.6 %	6.7 %	OR 1.33 (0.90, 1.96)	0.1539
Not treatment failure[3]	74.4 %	83.0 %	8.5 %	OR 1.65 (1.03, 2.63)	0.0364
PERR at Week 52[1] Responders	35.4 %	46.6 %	11.2 %	OR 1.59 (1.06, 2.38)	0.0245
Time to renal-related event or death[1] Percentage of patients with event[2] Time to event [Hazard ratio (95 % CI)]	28.3 %	15.7 %	- -	 HR 0.51 (0.34, 0.77)	 0.0014

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

[2] When excluding deaths from the analysis (1 for Benlysta; 2 for placebo), the percentage of patients with a renal-related event was 15.2 % for Benlysta compared with 27.4 % for placebo (HR = 0.51; 95 % CI: 0.34, 0.78).

[3] Treatment failure: Patients who took protocol-prohibited medication.

SUMMARY OF PRODUCT CHARACTERISTICS

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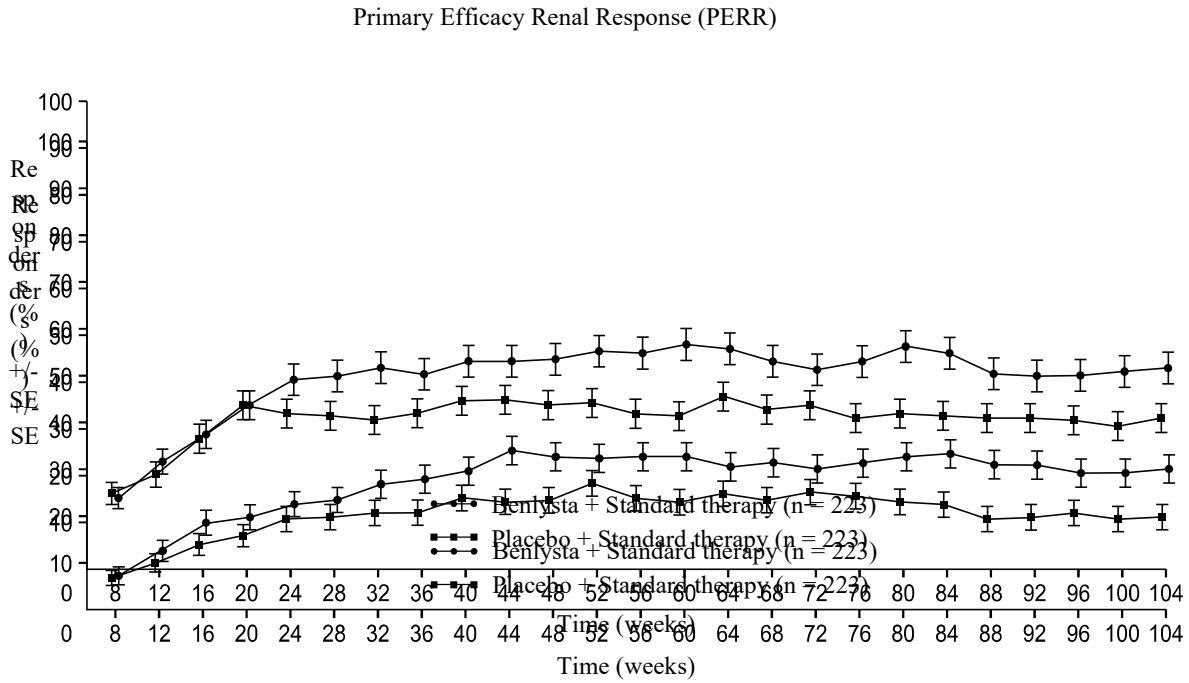
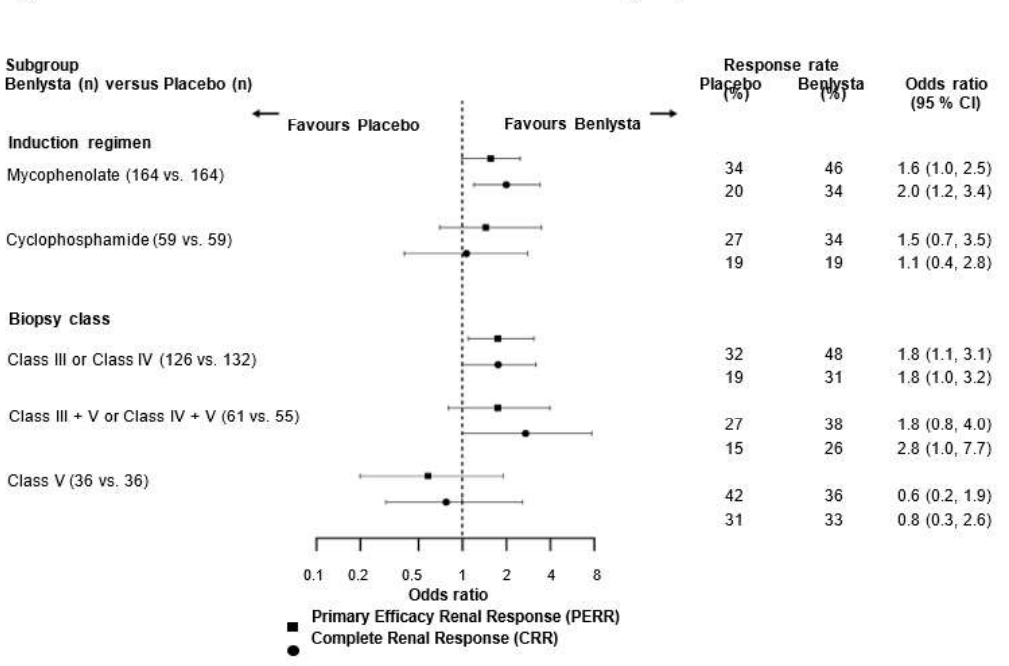
A numerically greater percentage of patients receiving Benlysta achieved PERR beginning at Week 24 compared with placebo, and this treatment difference was maintained through to Week 104. Beginning at Week 12, a numerically greater percentage of patients receiving Benlysta achieved CRR compared with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

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



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

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



Age and race

There were no

observed differences in efficacy or safety in SLE patients ≥ 65 years who received Benlysta intravenously or subcutaneously compared to the overall population in placebo-controlled studies; however, the number of patients aged ≥ 65 years (62 patients for efficacy and 219 for safety) is not sufficient to determine whether they respond differently to younger patients.

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

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

Paediatric population

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

5.2 Pharmacokinetic properties

The subcutaneous pharmacokinetic parameters below are based on population parameter estimates from 661 subjects, comprised of 554 SLE patients and 107 healthy subjects, who received Benlysta subcutaneously.

Absorption

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

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

Distribution

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

Biotransformation

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

Elimination

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

SUMMARY OF PRODUCT CHARACTERISTICS

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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, due to renal disease activity, belimumab clearance was initially higher than observed in SLE studies; however, after 24 weeks of treatment and throughout the remainder of the study, belimumab clearance and exposure were similar to that observed in adult patients with SLE who received belimumab 10 mg/kg intravenously.

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

Special Patient Populations

Paediatric population: No pharmacokinetic data are available for subcutaneous administration of Benlysta in paediatric patients.

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

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

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

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

Body weight/Body mass index (BMI)

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

Transitioning from intravenous to subcutaneous administration

SLE
Patients 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 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.

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 4.2).

5.3 Preclinical safety data

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

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

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

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

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

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Arginine hydrochloride
Histidine
Histidine monohydrochloride
Polysorbate 80
Sodium chloride
Water for injections

SUMMARY OF PRODUCT CHARACTERISTICS

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6.2 Incompatibilities

None known.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

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

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

6.5 Nature and contents of container

Pre-filled pen

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

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

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

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

7 MARKETING AUTHORISATION HOLDER

GlaxoSmithKline UK Limited

980 Great West Road

Brentford

Middlesex

TW8 9GS

Certificate Number: PP10191843

SUMMARY OF PRODUCT CHARACTERISTICS

Printed for Certificate of Pharmaceutical Product

United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 19494/0271

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01/01/2021

10 DATE OF REVISION OF THE TEXT

02/12/2024