HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

29 February 2012

BENLYSTA 120 mg, powder for concentrate for solution for infusion
Vial of 120 mg (CIP code: 580 875-8)

BENLYSTA 400 mg, powder for concentrate for solution for infusion
Vial of 400 mg (CIP code: 580 876-4)

Applicant: GLAXOSMITHKLINE

Belimumab
ATC code: L04AA26 (selective immunosuppressants)

List I
Medicinal product reserved for hospital use. Prescription restricted to internal medicine, rheumatology, nephrology or dermatology specialists.

Date of Marketing Authorisation (centralised procedure): 13 July 2011

Reason for request: Inclusion on the list of medicines approved for hospital use.

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Belimumab

1.2. Background

BENLYSTA is the first anti-BLyS indicated in the treatment of systemic lupus erythematosus (SLE). It is a specific antibody for the BLyS (soluble human B Lymphocyte Stimulator protein). By blocking the binding of the BLyS soluble protein to its receptors on B lymphocytes, BENLYSTA inhibits their survival and their differentiation.

1.3. Indication

"BENLYSTA (belimumab) 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."

1.4. Dosage

"BENLYSTA (belimumab) treatment should be initiated and supervised by a qualified physician experienced in the diagnosis and treatment of SLE. BENLYSTA (belimumab) infusions should be administered by a qualified healthcare professional trained to give infusion therapy. Administration of BENLYSTA (belimumab) may result in hypersensitivity reactions and infusion reactions. Therefore, BENLYSTA (belimumab) should be administered in an environment where resources for managing such reactions are immediately available

There are no or insufficient data available on the effects of BENLYSTA (belimumab) in patients with severe active lupus nephritis or severe active central nervous system lupus (CNS). Therefore, BENLYSTA (belimumab) cannot be recommended to treat these forms of SLE.

Posology

Premedication including an antihistamine, with or without an antipyretic, may be administered before the infusion of BENLYSTA (belimumab).

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

Special populations

Elderly (>65 years)
The efficacy and tolerance of BENLYSTA (belimumab) in the elderly has not been established. Data on patients older than 65 years are limited to less than 1.6% of the studied population. The use of BENLYSTA (belimumab) in elderly patients is not recommended unless the benefits are expected to outweigh the risks. In case the administration of BENLYSTA (belimumab) to elderly patients is deemed necessary, dose adjustment is not required.

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 for this population.

Hepatic impairment
No specific studies with BENLYSTA (belimumab) have been conducted in patients with hepatic impairment. Patients with hepatic impairment are unlikely to require dose adjustment.

Paediatric population

The safety and efficacy of BENLYSTA (belimumab) in children (less than 18 years of age) has not been established. No data are available.

Method of administration

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

BENLYSTA (belimumab) should be infused over a one hour period.

BENLYSTA (belimumab) 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."

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2011)

L : Antineoplastic and immunomodulating agents
L04 : Immunosuppressants
L04A : Immunosuppressants
L04AA : Selective immunosuppressants
L04AA26 : Belimumab

2.2. Medicines in the same therapeutic category

BENLYSTA is the only medicinal product in the anti-BLyS category indicated for SLE.

2.3. Medicines with a similar therapeutic aim

Other medicinal products used for systemic lupus erythematosus are:

Disease-modifying treatments:
- Amino-4-quinolines (antimalarials)
- Corticosteroids, used at low doses (off-label use) as a disease modifying treatment for systemic lupus erythematosus.

Specific treatments:
- Amino-4-quinolines (antimalarials)
- Topical corticosteroids
- Systemically administered corticosteroids
- NSAIDs and analgesics
- Immunosuppressants:
  - azathioprine
  - cyclophosphamide
  - thalidomide (off-label use, but authorisation for reimbursement over-ridden within the framework of Article L162-17-2-1 of the French Social Security Code in the treatment of cutaneous lupus erythematosus resistant to traditional treatments – OG of 20/10/09)
  - tacrolimus (off-label use)
  - methotrexate (off-label use)
  - ciclosporine (off-label use)
  - mycophenolate mofetil (off-label use)

3 ANALYSIS OF AVAILABLE DATA

The assessment of the efficacy and tolerance of belimumab is based on two phase III studies versus placebo, with similar protocols:

- BLISS 52 (study lasting 52 weeks)
- BLISS 76 (study lasting 76 weeks)

3.1. Efficacy

BLISS 52 and BLISS 76 Studies:
These two randomised, double blind studies compared two doses of belimumab (1 and 10 mg/kg) with placebo, in combination with standard treatment, in SLE patients over a 52 (BLISS 52) or 76 week period (BLISS 76).

Inclusion criteria:
- patients aged 18 years or older,
- a systemic lupus diagnosis as defined by the 1997 classification criteria of the ACR (*American College of Rheumatology,* see Appendix 1),
- **and** active SLE as defined by a SELENA-SLEDAI[1] score ≥ 6 at screening;
- **and** a positive anti-nuclear antibody (ANA) (ANA titre ≥ 1:80) and/or positive anti-ds DNA antibodies (≥ 30 units/ml) at two time points prior to randomisation
- **and** receiving standard treatment for lupus that has remained unchanged at a stable dose for at least 30 days.

Main non-inclusion criteria:
- severe active lupus nephritis as defined by a proteinuria > 6 g/24 hours or equivalent level according to the proteinuria/creatininuria ratio or a serum creatinine level of 2.5 mg/dl or active nephritis or patients that needed haemodialysis or received a high dose of prednisone (> 100 mg/day) within the 90 days prior to the first day of treatment (Day 0);
- severe active central nervous system lupus, (epilepsy, psychosis, organic brain syndrome, vascular accident, encephalitis or vasculitis due to CNS) requiring therapeutic intervention in the two months prior to Day 0;
- pregnancy;
- previous history of lymphocyte B targeting treatments;
- any experimental medicinal product within the 60 days prior to Day 0 for non biological products and within the previous year for biological products or abatacept;
- cyclophosphamide IV (6 months before Day 0);
- anti-TNF treatment;
- interleukin-1 receptor inhibitor, IV Immunoglobulin (IVIG), prednisone >100 mg/ day or plasmapheresis whithin the 3 months before Day 0;
- administration of a live vaccine within 30 days before Day 0;
- previous medical history of major organ or stem cell transplants.

Treatments:
- belimumab 1 mg/kg
- belimumab 10 mg/kg (dose retained in Marketing Authorisation)
- placebo

[1] "Safety of Estrogen Lupus Erythematosus National Assessment - Systemic Lupus Erythematosus Disease Activity Index": see definition in Appendix 2

Belimumab and the placebo were administered by IV injection (infusion over one hour) on Day 0, Day 14, Day 28 then every 28 days up to Week 48 in the BLISS 52 study, and up to Week 72 in the BLISS 76 study.
Patients could receive belimumab in combination with their standard treatments, which included at least one of the following treatments: NSAIDs, antimalarials, corticosteroids and immunosuppressants. The standard treatment needed to be stable for at least 30 days upon entry in the study. Adjustments to the standard treatment during the study were allowed according to the predefined rules stated in the protocol.
Patients who required changes in standard treatment for their SLE background medications beyond that permitted bythe protocol were declared as treatment failures/non-responders.

Primary efficacy endpoint:
The primary efficacy endpoint is a composite endpoint, the SLE Responder Index (SRI) measured at 52 weeks, defined by the percentage of patients responding simultaneously to the following three conditions:

• reduction of at least 4 points in SELENA-SLEDAI[1]

AND

• no new system or organs affected as defined by one BILAG[2] A item or two BILAG B items

AND

• no worsening in overall condition of patient‘s health according to the judgement of the doctor, the worsening in condition being defined by an increase > 0.30 points on the PGA scale.[3]

Note: there is currently no consensus on the reduction of at least 4 points in the SELENA-SLEDAI score defining a clinical relevance threshold for this score.

Results:

BLISS 52 Study
A total of 867 patients were included, of which 865 received at least one dose of treatment. These patients constituted the modified ITT population used in the analysis of the results.

The overall rate of premature discontinuation was 21% in the placebo group and 17% for each of the belimumab 10 and 1 mg/kg groups.
The most frequent reasons for discontinuing the study were adverse events (6.6% in the placebo group vs. 5.2% and 5.6% in the belimumab 10 and 1 mg/kg groups) and lack of efficacy (5.6% in the placebo group vs. 4.1% and 4.2% in the belimumab 10 and 1 mg/kg groups).

The baseline patient characteristics were comparable across the three groups.
The majority of patients included were female (95%) with a mean age of 35 years. The mean duration of SLE evolution was 5.3 years and the mean SELENA-SLEDAI score was 9.75 points. The percentage of patients with a score ≥ 10 (high to very high activity) was 54%. Patients were already receiving treatment with corticosteroids in 96.0% of cases (of which 69.4% had a dose > 7.5 mg/day), antimalarials (67.2%) and immunosuppressants (42.2%).

After 52 weeks of treatment, the percentage of SRI responders was significantly higher in the belimumab groups than in the placebo group (see table 1).

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[2] "British Isles Lupus Assessment Group": see definition in Appendix 3

[3] "Physician Global Assessment". Score of 0 to 3: no activity (0), mild activity (1), moderate activity (2-2.5), potentially fatal activity (3). An increase of 1 point compared with the last evaluation is considered as a mild to moderate flare and an increase of more than 2.5 points is considered as a serious flare.

Table 1: Results for the percentage of SRI responders at 52 weeks (BLISS 52 study)

	Placebo **N = 287**	**Belimumab** **10 mg/kg** **N = 290**	**Belimumab** **1 mg/kg** **N = 288**
SRI Responders (%)	43.6	57.6	51.4
Difference vs. placebo	-	+14.03	+7.83
p	-	0.0006	0.0129

BLISS 76 Study

A total of 826 patients were included, of which 819 received at least 1 dose of treatment. These patients constituted the modified ITT population used in the analysis of results.

The overall rate of premature discontinuation was 26% in the placebo group, 23% in the belimumab 10 mg/kg group and 20% in the 1 mg/kg group.
Patients discontinued the study prematurely at their own request in the majority of cases, which was higher in the placebo group (24%) than in the belimumab groups (14% for the 1 mg/kg dose and 13% for the 10 mg/kg dose).
The percentage of discontinuation due to a lack of efficacy was similar across the three groups (5 to 5.5%). Discontinuation due to an adverse event was 7.0% in the belimumab 10 mg/kg group, 4.8% in the belimumab 1 mg/kg group and 5.8% in the placebo group.

The baseline patient characteristics were comparable across the three groups.
The majority of patients included were female (93.3%) with a mean age of 40 years. The duration of SLE evolution was 7.5 years and the mean SELENA-SLEDAI score was 9.66 points. The percentage of patients with a score ≥ 10 (high to very high activity) was 51%. Patients were already receiving treatment with corticosteroids in 76.0% of cases (of which 45.9% had a dose > 7.5 mg/day), antimalarials (63.4%) and immunosuppressants (55.6%).

After 52 weeks of treatment, the percentage of SRI responders (primary efficacy endpoint) was significantly higher in the belimumab 10mg/kg group than in the placebo group (see table 2).

After 76 weeks of treatment, the percentage of SRI responders was 39.6% with belimumab 10 mg/kg and 27.5% with placebo, with a difference of 12.1%.

Table 2: Results for the percentage of SRI responders at 52 weeks (BLISS 76 study)

	Placebo **N = 275**	**Belimumab** **10 mg/kg** **N = 273**	**Belimumab** **1 mg/kg** **N = 271**
SRI Responders (%)	33.8	43.2	40.6
Difference vs. placebo	-	+ 9.41	+ 6.77
p	-	0.0207	0.1041

Pooled analysis of the BLISS 52 and BLISS 76 studies

Across these two studies, 1,684 patients were included, with a mean age of 37.8 years, the large majority of whom were female (94%).
Their condition had been evolving for a mean duration of 6.4 years, with a SELENA-SLEDAI score ≥ 10 for 52.1% of patients. Patients were already receiving corticosteroid treatment in 86.3% of cases (of which 58.0% had a dose > 7.5 mg/day), antimalarials (65.3%) and immunosuppressants (48.7%).

After 52 weeks of treatment, the percentage of SRI responders was significantly higher in the belimumab 10 mg/kg group than in the placebo group (50.6% with belimumab vs. 38.8% with placebo *i.e.* a difference of 11.8% ($p < 0.0001$).

Results for the high disease activity sub-group of patients (severity criterion used in the indication validated by the Marketing Authorisation)
This analysis was carried out post hoc, at the request of the EMA.
The population of patients with high disease activity can be defined by the presence of one or several of the following characteristics:
- SELENA-SLEDAI score ≥ 10
- positive anti-ds DNA auto-antibodies
- low C3 or C4 serum complement levels
- requiring systemic corticosteroid treatment to manage the disease

The results obtained from this analysis combined the BLISS 52 and BLISS 76 studies into three sub-groups:
- patients with a SELENA-SLEDAI score≥ 10
- patients using corticosteroids and with low C3/C4 levels at baseline
- patients with low C3/C4 levels and anti-ds DNA auto-antibodies

For each of these sub-groups, the percentage of SRI responders was significantly higher in patients treated with belimumab 10 mg/kg than for patients in the placebo group (see table 3) with differences of around 20% compared with placebo.

Table 3: Results in terms of percentage of SRI responders based on the sub-groups of patients with high SLE activity

Sub-groups of patients:	**Placebo**	**Belimumab 10 mg/kg**
SELENA-SLEDAI score ≥ 10 (52% of total number*)	N = 298	N = 296
SRI Responders (%)	44.3	63.2
Difference vs. placebo	-	**18.9**
p	-	< 0.0001
Corticosteroids use and low C3/C4 (56% of total number*)	N = 309	N = 327
SRI Responders (%)	32.4	53.0
Difference vs. placebo	-	**21.1**
p	-	< 0.0001
low C3/C4 and presence of anti-ds DNA auto-antibodies (52% of total number*)	N = 287	N = 305
SRI Responders (%)	31.7	51.5
Difference vs. placebo	-	**19.8**
p	-	< 0.0001

*: total number in placebo group + belimumab 10 mg/kg group

3.2. Adverse effects

3.2.1. Data from clinical studies:

Tolerance data from the comparative studies versus placebo showed that nausea (15.1% with belimumab 10 mg/kg vs. 12.6% with the placebo), diarrhoea (12.2% vs. 9.9%) and fever (9.6% vs. 7.9%) were very frequent.

Gastrointestinal problems were more common in obese patients (BMI < 30 kg/m^2) than for those with a normal weight (18,5 kg ≤ BMI ≤ 30 kg/m^2).

Infusion-related reactions, including hypersensitivity, were very common (16.9% vs. 14.7%) and required treatment discontinuation in 1% of patients treated with belimumab vs. 0.3% of patients on placebo.

Other common adverse events were infections, psychiatric disorders, peripheral oedemas and pains in extremities and leucopoenia.

The overall incidence of infections was 70% for patients treated with belimumab and 67% of patients on the placebo. These infections were primarily urinary (13.4% vs. 12.7%), rhinopharyngitis (9.8% vs. 7.3%), bronchitis (9.2% vs. 5.3%), gastroenteritis (7.4% vs. 6.2%) and cystitis (4.0% vs. 2.8%).
Five percent of patients receiving belimumab or the placebo had a serious infection; the discontinuation of treatment was necessary for 0.6% of patients receiving belimumab and 1% of patients on the placebo.

Serious infections, observed in the two groups, were pneumonia, lower urinary tract infections, bacteraemia/septicaemia, cellulitis, upper urinary tract infections and bronchitis (see table 4).

Table 4: The most common serious infections (occurring in at least three patients in at least one treatment arm)

Type of serious infection	Placebo n = 675	Belimumab 10 mg/kg n = 674
Total number of serious infections – n (%)	37 (5.5)	36 (5.3)
• Pneumonia	11[*] (1.6)	8[*] (1.2)
• Lower urinary tract infection	5 (0.7)	6 (0.9)
• Bacteraemia /Sepsis	2[3] (0.3)	5[3] (0.7)
• Cellulitis	3 (0.4)	1 (0.1)
• Upper urinary tract infection	4 (0.6)	2 (0.3)
• Bronchitis	1 (0.1)	3 (0.4)

*: 2 serious cases of pneumonia (1 case in the placebo arm and 1 case in the belimumab 10 mg/kg arm) occurred more than 8 weeks after the last dose of treatment and were considered as being related to the study treatment by the clinical study investigator.

During the three randomised comparative studies (one phase II study and two phase III studies), no cases of opportunistic infection were reported for patients on placebo versus three cases (two serious and one non-serious) with belimumab. In one of these cases, the causal relationship appears to be unlikely, with the infection being declared on the day of the first infusion. During the long-term, open-label study extensions (where all patients received belimumab), 6 cases were reported in patients initially treated with belimumab, with no cases for patients who initially received the placebo. The incidence of opportunistic infections occurring was 0.20 patients per 100 patient-years, calculated from the comparative studies and 0.23 calculated from all of the studies including the long-term extension phases. Currently, no increase in risk of opportunistic infection linked with the duration of exposure appears. There also does not appear to be an increased risk, compared with the normal incidence, in patients with SLE.

Insomnia (7.0% vs. 5.5%), depression (5.8% vs. 4.0%) and anxiety (2.2% vs. 2.8%) were also observed.

Pain in extremity was experienced by 6.4% of patients treated with belimumab and 4.3% of patients on placebo.

Leucopoenia was observed in 3.7% of patients treated with belimumab and 2.5% of patients on placebo.

No increased risk of cancer was observed; however, a greater risk cannot be excluded and must be evaluated in the long-term.

3.2.2. Risk management plan

The risk management plan indicates the carry-out of a long-term, comparative study versus placebo (5 years), which must include 5,000 patients, to evaluate the longer-term infection and cancer risks.

3.3. Conclusion

The efficacy and tolerance of belimumab were evaluated in two randomised, comparative phase III studies (BLISS 52 and BLISS 76) versus placebo, in patients with active SLE at inclusion according to the *American College of Rheumatology* diagnostic characteristics and characterised by:

- a SELENA-SLEDAI score ≥ 6 at screening,
- and a positive anti-nuclear antibody (ANA) (ANA titre ≥ 1:80),
- and/or positive anti-ds DNA antibodies (≥ 30 units/ml) at two time points prior to randomisation,
- and receiving standard stable standard SLE treatment (comprising at least one of the following treatments: NSAIDs, antimalarials, corticosteroids, immunosuppressants) and at a stable dose for at least 30 days. Adjustments to the standard treatment during the study were allowed in accordance with the predefined rules stated in the protocol. Patients requiring changes in standard treatment for their SLE beyond those authorised in the protocol were declared as treatment failures/non-responders.

A total of 1,684 patients were included, divided into three groups: belimumab 10 mg/kg, belimumab 1 mg/kg (dosage not retained in Marketing Authorisation) and placebo. The study treatments were administered by IV infusion over one hour every 28 days up to 48 weeks in the BLISS 52 study and up to 72 weeks in the BLISS 76 study. The primary efficacy endpoint was the percentage of SRI responders (SLE Responder Index) measured at 52 weeks in the two studies.
The percentage of SRI responders is defined by the percentage of patients simultaneously satisfying the following three conditions:

- reduction of at least 4 points in SELENA-SLEDAI score
- no new system or organs affected as defined by one BILAG A item or two BILAG B items
- no worsening in overall condition of patient's health according to the judgement of the doctor, the worsening in condition being defined by an increase of > 0.30 points on the PGA scale.

The percentage of SRI responders at 52 weeks was higher with belimumab 10 mg/kg than with the placebo:

- BLISS 52 study: 57.6% vs. 43.6%, *i.e.* a difference of 14.03% (p = 0.0006)
- BLISS 76 study: 43.2% vs. 33.8%, *i.e.* a difference of 9.41% (p = 0.0207)
- pooled analysis of the two studies: 50.6% vs. 38.8%, *i.e.* a difference of 11.8% (p<0.0001).

These differences observed in favour of belimumab, despite being statistically significant, are modest.

A pooled analysis of two studies, carried out *a posteriori* at the request of the EMA, was performed on three sub-groups of patients with characteristics that may define a severe form of the disease. In these three sub-groups, the differences, in terms of the percentage of SRI responders at 52 weeks in favour of belimumab versus placebo were greater than in the total population of the studies:

- SELENA-SLEDAI score ≥ 10: 18.9%
- corticosteroids use and low C3/C4 levels at baseline: 21.1%
- low C3/C4 levels and anti-ds DNA auto-antibodies: 19.8%.

The most common adverse events with belimumab were diarrhoea (12.2% vs. 9.9% with placebo), nausea (15.1% vs. 12.6%), infections (70% vs. 67%), fever (9.6% vs. 7.9%), infusion-related reactions, including hypersensitivity reactions (16.9% vs. 14.7%), psychiatric disorders (insomnia, depression and anxiety), leucopoenia and pain in extremity.
The risks of infection, especially opportunistic infections, and the occurrence of cancers must be monitored. The risk management plan indicates the carry-out of a long-term, comparative study versus placebo (5 years), which must include 5,000 patients, to evaluate the longer-term infection and cancer risks.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

SLE is an auto-immune disease that varies from person to person, mainly affecting women during the period of active ovulation (9 women for 1 man), is polymorphic, evolving through flares of varying severity and may be life-threatening.

This medicine is intended as symptomatic treatment.

Public health benefit

Systemic lupus erythematosus is a rare condition. The burden of this disease is therefore small, as the one for the population stated in the indication.

There is a recognised public health need (Second Plan “Rare diseases 2011-2014”).

Given the data available, the impact of BENLYSTA on the morbidity and mortality of patients treated is small and there is no impact on their quality of life. Furthermore, BENLYSTA is not expected to have an impact on the organisation of healthcare.

The transferability of results from studies to current practice is questionable, especially due to the exclusion of patients with severe renal and neurological affections in the studies, and doubts as to the long-term tolerance profile (especially the risk of cancer) of this monoclonal antibody.

In addition, BENLYSTA only provides a partial response to the identified public health need.

Consequently, no public health benefit is expected from BENLYSTA in this indication.

The efficacy/adverse effects ratio is moderate.

This medicinal product is a second-line treatment in the management of active forms of SLE in adults, with auto-antibodies and a high degree of disease activity (e.g. positive anti-ds DNA and low complement) co-administered with standard treatment, after failure or intolerance of a previous treatment (antimalarials, NSAIDs, corticosteroids and/or immunosuppressants according to the affected organ systems). Given the absence of data concerning severe renal and neurological affections, it is not recommended to prescribe belimumab in these forms of lupus.

There are no validated therapeutic alternatives in cases of failure of or intolerance to a treatment including synthetic antimalarials, NSAIDs, corticosteroids or immunosuppressants.

The actual benefit of BENLYSTA 120 mg and 400 mg, powder for concentrate for solution for infusion is substantial.

4.2. Improvement in actual benefit (IAB)

Given its modest efficacy, the absence of data for severe forms of renal and neurological affections and uncertainties concerning its long-term tolerance profile, the improvement in actual benefit of BENLYSTA, in combination with standard treatment, is minor (IAB IV) in the management of adult patients with active SLE with auto-antibodies and a high degree of disease activity despite treatment with antimalarials, NSAIDs, corticosteroids and/or immunosuppressants according to the affected organ systems.

4.3. Therapeutic use

4.3.1. Therapeutic strategy

The disease-modifying treatment for systemic lupus, the aim of which is the prevention of relapses, is antimalarials (chloroquine, hydroxychloroquine) and/or low dose corticosteroids (if corticosteroid treatment is started due to a flare).

Immunosuppressant agents or immunomodulators, with a Marketing Authorisation for SLE such as azathioprine and cyclophosphamide or those without a Marketing Authorisation in this indication such as leflunomide, methotrexate, mycophenolate mofetil and ciclosporine, are used in the most severe or the most active forms of the disease, poorly controlled by antimalarials and low dose corticosteroids, or for forms requiring the prolonged use of corticosteroids. The choice of treatment is based on the type of affection and its severity (see PNDS-LTC 21, January 2010).

For more severe forms, high dose corticosteroids are usually prescribed. Topical corticosteroids may be used to treat forms affecting the skin.

NSAIDs and analgesics may be of benefit in less severe forms affecting the bones and joints.

Thalidomide has authorisation for reimbursement overridden within the framework of Article L162-17-2-1 of the French Social Security Code (Official Gazette of 20/10/09) in the treatment of cutaneous lupus erythematosus resistant to traditional treatments.

If the disease is severe or resistant to treatment, combining therapies is common.

4.3.2. Role of the medicinal product

BENLYSTA is a second-line treatment, in combination with standard treatment, for active systemic lupus with auto-antibodies and a high degree of disease activity after failure or intolerance of a previous treatment appropriately monitored (antimalarials, NSAIDs, corticosteroids and/or immunosuppressants according to the affected organ systems). It is for adult use only. This medicinal product is more specifically used in the treatment of moderate to severe forms of the disease.
Belimumab has not been studied in severe renal and neurological affections. Consequently, it is not recommended to prescribe BENLYSTA in these forms of lupus.

4.4. Target population

The target population of BENLYSTA is defined as adult patients with active SLE, auto-antibodies and a high degree of disease activity despite standard treatment (antimalarials, NSAIDs, corticosteroids and/or immunosuppressants according to the affected organ systems).

Systemic lupus:
According to data from the general healthcare system on those affected long-term by the condition on 31 December 2010,[4] the rate of prevalence of systemic lupus erythematosus (code CIM-10 M32) is estimated as 43 cases/100,000 people, *i.e.* 27,000 patients based on the French population on 1st January 2012.[5]

[4] Frequency of LTC of 31/12/2010. source: http://www.ameli.fr
[5] Source: http://www.insee.fr

Active disease:
There are no published epidemiological data that allow the proportion of patients with active systemic lupus and a high degree of disease activity to be estimated.
A European observational study carried out by the company (non-published ancillary LUCIE study) estimated that, among adult patients with systemic lupus that have been subject to medical consultation, 29% of them were presenting with active lupus, defined as having persistent disease activity over the last 12 months AND positive auto-antibodies (ANA and/or anti-ds DNA) AND treated for their SLE (corticosteroids, NSAIDs, antimalarials, immunosuppressants or biotherapies).
Consequently, the population of adult patients with active systemic lupus with positive auto-antibodies despite standard treatment can be estimated at 7,900 patients.

High degree of disease activity:
A high degree of disease activity can be determined via different clinical or biological analysis criteria, which may be combined. According to data from the two phase III clinical studies that included patients with active SLE, the percentage of patients meeting these criteria were as follows:
- low C3 or C4 serum complement: 62%;
- anti-ds DNA antibodies: 69%;
- SELENA-SLEDAI score ≥ 10: 52%;
- anti-ds DNA antibodies and low complement levels: 52% ;
- anti-ds DNA antibodies and low complement levels and/or a SELENA-SLEDAI score ≥ 10: 70%;
- corticosteroids use: 86%.

Thus, it may be considered that between 52% and 86% of patients had a high degree of disease activity. The population of adult patients with active SLE, positive for auto-antibodies and a high degree of disease activity despite standard treatment would be between 4,100 and 6,800 patients.

Renal and neurological forms of the disease:
According to the LUCIE study, among the patients with active SLE, 28% had renal affection and 6% had neurological affection. It may be estimated that 28% to 34% of patients with active systemic lupus had renal and/or neurological impairment.

Consequently, the target population of BENLYSTA defined as adult patients with active systemic lupus, positive for auto-antibodies, with a high degree of disease activity despite standard treatment and not having severe renal and neurological affection would be between 2,700 and 4,900 patients.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines approved for hospital use and various public services in the indications and at the dosages in the Marketing Authorisation.

The Committee would like to re-evaluate BENLYSTA after 2 years.

The Committee requests that a significant number of French patients are included in the long-term studies versus placebo stipulated in the RMP and with the aim of evaluating the long-term infection and cancer risks. The number of patients included should be enough so that it is representative of the French situation.

Packaging: Appropriate for the prescription conditions.

<u>APPENDIX 1</u>: Classification criteria of the *American College of Rheumatology* for systemic lupus

According to ACR recommendations (1999), systemic lupus in adults should be suspected when the patient presents with two or more characteristics included in the table below. A diagnosis of SLE is proposed if **at least four of these criteria** are present.

Criteria	Definition
Malar rash	Fixed erythema, flat or raised, mainly to the cheeks and nose, also potentially affecting the nasolabial folds and the eyelids.
Discoid lupus	Erythematous areas threaded with fine telangiectasia, thick scaly patches blocking the follicles and atrophy and scarring.
Photosensitivity	Skin eruptions following an abnormal reaction to sunlight, as determined by the patient's previous medical history or observed by doctors
Oral or nasopharyngeal ulcers	Oral or nasopharyngeal ulcers, not normally painful, observed by the doctor.
Arthritis	Nonerosive arthritis affecting at least 2 peripheral joints, characterised by swelling, sensitivity or effusion.
Serositis	Pleurisy, following previous history of pleural pain, auscultatory abnormalities or evidence of a pleural effusion or Pericarditis documented by electrocardiography, auscultatory abnormalities, or evidence of a pericardial effusion.
Renal disorders	Persistent proteinuria > 0.5 g/day (or +++) or Urinary casts.
Neurological disorders	Convulsions or psychoses in the absence of inducing medication or Recognised metabolic disorders (e.g.: uraemia, ketoacidosis, and electrolyte imbalance).
Haematological effects	Haemolytic anaemia or Leucopenia < 4,000/µl observed from 2 measurements or Lymphocytopenia < 1,500/µl observed from 2 measurements or Thrombocytopenia < 100,000/µl in the absence of cytopenia medication.
Immunological disorder	Presence of anti-dsDNA or anti-Sm or antiphospholipids antibodies Positive Anti-dsDNA at an abnormal level or Presence of anti-Sm antibodies or Abnormal titre for anticardiolipin IgG or IgM antibodies or Presence of prothrombinase antibody or Known false positive syphilis screen for at least 6 months (VDRL+/TPHA-)
ANAs	Abnormal titre for anti-nuclear factors in the absence of inducing medication (by immunofluorescence or equivalent analysis)

APPENDIX 2: SLEDAI/SELENA-SLEDAI

SLEDAI is a validated and weighted index to evaluate the activity of SLE. The disease activity is evaluated in nine systems based on clinical signs and symptoms, laboratory tests and a doctor's assessment. The method does not count subjective symptoms, such as fatigue, which is one of the most common constitutional symptoms of the disease. The clinical signs are taken into consideration if they are present at the time of the consultation visit or in the previous 10 days (Griffiths, 2005[6]). The weighted scores per organ (24 items in total) are added together as follows:

- central nervous system and vascular effects: score of 8 for each item
- renal system and musculoskeletal system: score of 4 for each item
- serosal, dermal and immunological tests: score of 2 for each item
- constitutional symptoms and haematological system: score of 1 for each item.

SELENA-SLEDAI is a modified version of SLEDAI. The description of certain parameters is slightly modified, but the systems/organs and the weighted scores are the same as for SLEDAI. SELENA-SLEDAI measures the presence or absence of clinical signs, symptoms or anomalies in laboratory test results for SLE. It does not take into consideration the evolution of signs and symptoms (improvement or worsening) compared with the previous consultation visit. Consequently, SELENA-SLEDAI is not very sensitive to changes, as a full determination of signs or symptoms is required to show a change in activity of the disease. Furthermore, SELENA-SLEDAI only includes assessment of two biomarkers related with SLE activity (complement levels and presence of anti-ds DNA). Neither the other auto-antibodies or BLyS levels (which are correlated to the activity of the disease and its clinical signs) are evaluated with SELENA-SLEDAI (Bombardier, 1992[7]).

The maximum theoretical SLEDAI score is 105 (if the patient simultaneously presents with all 24 clinical or biological signs – an inconceivable situation in practice). A score ≥ 20 corresponds to a "very high activity" of systemic lupus.

The categories of disease activity are defined based on SLEDAI scores, as follows (Petri, 1999[8]):

- SLEDAI 0 = no activity
- SLEDAI 1-5 = mild activity
- SLEDAI 6-10 = moderate activity
- SLEDAI 11-19 = high activity
- SLEDAI ≥ 20 = very high activity

An SLE flare is defined by an increase of 3 points or more in SLEDAI or SELENA-SLEDAI score. An increase of more than 5 points is associated with the introduction of a new therapy or a modification in current treatment in more than 50% of the cases.

A reduction of 4 points or more in the SELENA-SLEDAI score is defined in the studies as a clinically relevant reduction in disease activity.

Note: this clinical relevance threshold is not currently the subject of a consensus of opinion.

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[6] Griffiths B, Mosca M, Gordon C. Assessment of patients with systemic lupus erythematosus and the use of lupus disease activity indices. Best Practice & Research Clinical Rheumatology. Vol. 19, No. 5, pp. 685–708, 2005.

[7] Bombardier C, Gladman DD, Urowitz MB, Caron D, Chang CH, and the Committee on prognosis studies in SLE. Derivation of the sledai. A disease activity index for lupus patients. Arthritis and Rheumatism, vol 35, no. 6 (June 1992).

[8] Petri M, Buyon J and Kim M. Classification and definition of major flares in SLE clinical studies. Lupus (1999) 8, 685-691.

APPENDIX 3: BILAG

The BILAG index is a clinical measurement of activity of systemic lupus. It is a score validated on the basis of experts' opinion. Unlike SELENA-SLEDAI, disease activity in eight different systems/organs is counted separately (general, mucocutaneous, neurological, musculoskeletal, cardiorespiratory, vascular, renal and haematological). The index comprises 86 items and includes renal and haematological results but not immunological tests (Griffiths, 2005[4]).

The score is based on the principle of a doctor's intention to treat a disease process:

- BILAG **A** (ACTION): serious effects of the disease requiring high dose corticosteroids (prednisone or equivalent ≥ 20 mg/day) and/or cytotoxic agents.
- BILAG **B** (BEWARE): more moderate effects of the disease requiring low dose corticosteroids, antimalarials or non-steroid anti-inflammatories (NSAIDs).
- BILAG **C** (CONTENTMENT): mild symptoms requiring only symptomatic treatment (i.e. analgesics or NSAIDs).
- BILAG **D** (DISCOUNT): no symptoms in an organ system that has previously been affected.
- BILAG **E** (No EVIDENCE): no symptoms in an organ system that has never been previously affected.

Numerical weighted scores are assigned to each of the scores above (A = 9, B = 3, C = 1 and D / E = 0), with a possible global score ranging from 0 to 72. However, the index was not initially designed for this purpose.

In this system, a severe flare (1A) is defined as an increase in any previous score to a BILAG A score in one or several organs/systems and a moderate flare (2B) is an increase from a BILAG C, D or E score to a B score in two systems/organs or more.

The development of a 1A or 2B flare is a clinically relevant change translated as sufficient deterioration in disease activity to justify an increase in treatment (Furie, 2009[9]).

[9] Furie RA et al, Novel evidence-based systemic lupus erythematosus responder index. ARTHRITIS Rhem 2009; 61: 1143-51.