Belimumab (Benlysta®) for the indication 'active, auto-antibody-positive systemic lupus erythematosus with a high degree of disease activity'
Pharmacotherapeutic report, summary

Approved on 23 April 2012 by the Medicinal Products Reimbursement Committee (CFH)

Medicine. Belimumab 120 mg, 400 mg, powder for concentrate for infusion. After reconstitution, the solution contains 80 mg belimumab per ml.

Registered indication. "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 treatment."

Posology. IV infusion: 10 mg/kg on days 0, 14 and 28, and at 4-week intervals thereafter. Belimumab should be infused over a 1-hour period. 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. Discontinuation of treatment with belimumab should be considered if there is no improvement in disease control after 6 months of treatment.

Mechanism of action. There is an association between plasma BLyS levels and SLE disease activity. Benlysta is a human IgG1 monoclonal antibody. It 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.

Summary of the therapeutic value

Intended effects. Based on results of the total study population, the EMA decided to register belimumab only for patients with a high degree of disease reactivity (e.g., positive anti-dsDNA and low complement). In a *post hoc* sub-group analysis, the difference in the response rate as measured by the SLE responder index was calculated in patients with a high degree of disease activity (positive anti-dsDNA and low complement). After 52 weeks' treatment, there was a 20% difference in the response rate between the "usual treatment regimen" and belimumab added to "the usual treatment regimen"), and a 12% difference after 76 weeks. This is higher than the response rate in the total study population (after 52 weeks there was a 12% difference and a 7% difference after 76 weeks). However, it is not clear at which cut-off point (in relation to the difference in response rate) a clinically relevant effect occurs. Furthermore, these data are based only on the values of one of the measuring instruments that can measure the degree of disease activity, namely, the SRI responder index. No data are available regarding the response rate as measured via the SELENA-SLEDAI index, the 'British Isles Lupus Assessment Group' (BILAG) and 'physician global assessment' (PGA). Furthermore, there is insufficient evidence that the increase in the response rate can result in a clinically relevant effect. For instance, the difference in percentage of patients with reduced prednisone intake after 52 weeks' treatment with

belimumab vs. placebo was the same between the subpopulation with a high degree of disease activity (5%) and the total study population (6%). This also applies to the rate of severe flares and the FACIT-fatigue score.

Unintended effects. In general, the addition of 10 mg/kg belimumab to the "usual treatment of choice" is well tolerated. Patients treated with belimumab had a higher incidence of infusion-related reactions and hypersensitivity reactions in comparison with patients treated with placebo. However, the percentage of patients with severe related unintended effects and the percentage of dropouts due to side effects was distributed equally over both study arms. In total 6 patients (0.9%) died in the belimumab-arm and 3 patients (0.4%) in the placebo-arm.

Experience. Experience with belimumab is limited.

Applicability. Belimumab has not been studied in – and is therefore not recommended for – patients with: severe active lupus nephritis, or 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), or who have a history of major organ transplant or hematopoietic stem-cell/bone marrow transplant or renal transplant.

Ease of use. Belimumab should be administered intravenously on days 0, 14 and 28, and at 4-week intervals thereafter. Discontinuation of treatment with belimumab should be considered if there is no improvement in disease control after 6 months of treatment.

Final conclusion. The therapeutic value of adding belimumab to the standard treatment in the treatment of adult patients with active, autoantibody-positive SLE with a high degree of disease activity is comparable with that of "usual treatment of choice".