Swiss Summary of the Risk Management Plan (RMP) for

Benlysta

(Belimumab)

RMP Summary:	Version 2
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License holder:	GlaxoSmithKline AG, Münchenbuchsee

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimize them.

The RMP summary of Benlysta is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the “Arzneimittelinformation / Information sur le médicament” approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of Benlysta in Switzerland is the “Arzneimittelinformation / Information sur le médicament” (see www.swissmedic.ch) approved and authorized by Swissmedic.

GlaxoSmithKline AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of Benlysta.

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for BENLYSTA (belimumab)

This is a summary of the risk management plan (RMP) for Benlysta. The RMP details important risks of Benlysta, how these risks can be minimised, and how more information will be obtained about Benlysta's risks and uncertainties (missing information).

Benlysta's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Benlysta should be used.

This summary of the RMP for Benlysta should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Benlysta's RMP.

I. The medicine and what it is used for

Benlysta is authorised

- as an add-on therapy in patients aged 5 years and older with active, autoantibody positive systemic lupus erythematosus (SLE) with a high degree of disease activity (e.g. anti-dsDNA and low complement) despite standard therapy
- in combination with background immunosuppressive therapies for the treatment of adult patients with active lupus nephritis (LN)

Benlysta is available as a subcutaneous injection (SC) or an infusion (IV). The IV route is approved for use in patients aged 5 years and older with SLE and adult patients with active lupus nephritis, whilst the SC route is approved only in adults with SLE and adult patients with active lupus nephritis.

(see SmPC for the full indication). It contains belimumab as the active substance and it is given by IV or SC route.

Further information about the evaluation of Benlysta’s benefits can be found in Benlysta’s EPAR, including in its plain-language summary, available on the EMA website, under the medicine’s webpage:

https://www.ema.europa.eu/en/medicines/human/EPAR/benlysta

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Benlysta, together with measures to minimise such risks and the proposed studies for learning more about Benlysta's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;

- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Benlysta is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Benlysta are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered/taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Benlysta. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

List of important risks and missing information	
Important identified risks	Infections Psychiatric events including depression and suicidality
Important potential risks	Progressive multifocal leukoencephalopathy (PML) Malignancies
Missing information	Limited data in pregnant and lactating patients Limited data in elderly patients Limited data on long-term safety in paediatric patients Lack of data in SLE patients with severe active central nervous system (CNS) lupus

II.B Summary of important risks

Important identified risk **Infections**	
Evidence for linking the risk to the medicine	Clinical trial and post-marketing data
Risk factors and risk groups	Infections are a common source of morbidity and mortality in patients with autoimmune diseases such as SLE. In addition to the disease itself, the use of immunosuppressive agents such as steroids and cytotoxic agents (e.g., cyclophosphamide, azathioprine, and MMF)
Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.4, 4.8 This is a prescription only medicine. Additional risk minimisation measures: None
Additional Pharmacovigilance activities	Additional Pharmacovigilance activities: Analysis of additional safety data that may arise from ongoing studies, including serious infections and infections of special interest from ongoing open-label study BEL114055 in the pediatric population. Evaluation of data on serious infections including opportunistic infections, tuberculosis, and herpes zoster from long-term safety registry (BEL116543/SABLE) See II.C of this summary for an overview of the post- authorisation development plan.

Important identified risk **Psychiatric events including depression and suicidality**	
Evidence for linking the risk to the medicine	Clinical trial, post-marketing data and literature
Risk factors and risk groups	Unknown
Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.4, 4.8 This is a prescription only medicine. Additional risk minimization measures: None

Additional Pharmacovigilance activities	Additional Pharmacovigilance activities Prospective assessment of suicidality in randomised controlled trials and BEL116543/SABLE (5-year registry study) See Section II.C of this summary for an overview of the post- authorisation development plan.

Important potential risk **Progressive multifocal leukoencephalopathy**	
Evidence for linking the risk to the medicine	Clinical trial, post-marketing data and literature
Risk factors and risk groups	Infections, including PML, are common source of morbidity and mortality in patients with autoimmune diseases such as SLE. In addition to the disease itself, the use of immunosuppressive agents such as steroids and cytotoxic agents (e.g., cyclophosphamide, azathioprine, and MMF)
Risk minimisation measures	Routine risk minimisation measures: **The IV and SC SmPC**
	Routine activity includes appropriate labelling. Section 4.4 Special warnings and precautions for use of the SmPCs contains the EMA SmPC text agreed: Progressive multifocal leukoencephalopathy (PML) has been reported with Benlysta treatment for SLE. Physicians should be particularly alert to symptoms suggestive of PML that patients may not notice (e.g., cognitive, neurological or psychiatric symptoms or signs). Patients should be monitored for any of these new or worsening symptoms or signs, and if such symptoms/signs occur, referral to a neurologist and appropriate diagnostic measures for PML should be considered. If PML is suspected, further dosing must be suspended until PML has been excluded. This is a prescription only medicine. Additional risk minimisation measures: None
Additional Pharmacovigilance activities	Additional Pharmacovigilance activities: Evaluation of data on opportunistic infections, including PML, tuberculosis, and herpes zoster from long-term safety registry (BEL116543/SABLE) See Section II.C of this summary for an overview of the post- authorisation development plan.

Important potential risk **Malignancies**	
Evidence for linking the risk to the medicine	Clinical trial, post-marketing data and literature
Risk factors and risk groups	Patients with SLE typically receive a wide variety of immunosuppressive or cytotoxic agents which confer an increased risk of malignancy.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4 This is a prescription only medicine. Additional risk minimisation measures: None
Additional Pharmacovigilance activities	Additional Pharmacovigilance activities: Evaluation of data on malignancies, including haematological malignancies and nonmelanoma skin cancer from the long- term safety registry (BEL116543/SABLE) See Section II.C of this summary for an overview of the post- authorisation development plan.

Missing information **Limited data in pregnant and lactating patients**	
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.6 and 5.3 This is a prescription only medicine. Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Ongoing Belimumab & Lupus Pregnancy Study (213928/bMUM) in the United States and Canada. See Section II.C of this summary for an overview of the post- authorisation development plan.

Missing information **Limited data in elderly patients**	
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.2 and 5.2 This is a prescription only medicine. Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Analysis plan for BEL116559 has been agreed with EMA. See Section II.C of this summary for an overview of the post- authorisation development plan

Missing information **Limited data on long-term safety in paediatric patients**	
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.2 This is a prescription only medicine. Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Evaluation of long-term safety (adverse events of special interest, including infections, other autoimmune diseases, immunogenicity, and malignancies) in enrolled subjects in BEL114055 until 10 years after their first belimumab dose SLE paediatric studies agreed with EMA in IV and SC PIP. See Section II.C of this summary for an overview of the post- authorisation development plan.

Missing information **Lack of data in SLE patients with severe active CNS lupus**	
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4 This is a prescription only medicine. Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

The following studies are conditions of the marketing authorisation:

SABLE Safety Registry:

Post-Marketing observational programme for Benlysta (BEL116543)

Purpose of the Study:

To assess the effectiveness and safety of long-term treatment in patients receiving Benlysta compared to those who are not.

II.C.2 Other studies in post-authorisation development plan

***Belimumab & Lupus Pregnancy Study (bMUM)*:**

Prospective cohort study (213928/bMUM) of Benlysta exposed and unexposed pregnancies.

Purpose of the Study:

The primary objective is to evaluate pregnancy and infant outcomes following Benlysta exposure and health status of live born infants at 1 year.

Pooled Analysis of Belimumab Elderly Patients:

Pooled analyses of elderly patients (aged ≥ 65 years) who participated in select belimumab, clinical trials (BEL116559)

Purpose of the Study:

To determine the safety and effectiveness in elderly patients.