PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR BENEPALI

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

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

This summary of the RMP for Benepali 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 Benepali's RMP.

I. The medicine and what it is used for

Benepali is authorised for the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, non-radiographic axial spondyloarthritis, plaque psoriasis, and paediatric plaque psoriasis (see SmPC for the full indication). It contains etanercept as the active substance and it is given by injection.

Further information about the evaluation of Benepali's benefits can be found in Benepali'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/benepali

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

Important risks of Benepali, together with measures to minimise such risks and the proposed studies for learning more about Benepali'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 PL 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 the case of Benepali, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

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

II.A List of important risks and missing information

Important risks of Benepali are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. 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 Benepali. 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	Malignancy (including lymphoma and leukaemia) Serious and opportunistic infections (including TB, *Legionella, Listeria* and parasitic infection) Demyelinating disorders Aplastic anaemia and pancytopenia Congestive heart failure in adult subjects
Important potential risks	Encephalitis/leukoencephalomyelitis Progressive multifocal leukoencephalopathy Impaired growth and development in juvenile subjects Acute ischemic cardiovascular events in adult subjects
Missing information	Not applicable

II.B Summary of important risks

II.B.1 Important identified risks

Malignancy (including lymphoma and leukaemia)	
Evidence for linking the risk to the medicine	Study SB4-G31-RA; proposed Summary of Product Characteristics (SmPC) for Benepali, section 4.4 'Special warnings and precautions for use'; referenced scientific publications.
Risk factors and risk groups	Overall risk of malignancy including cutaneous and non-cutaneous cancers in subjects with RA and PsO has been reported to be higher than that observed in healthy subjects. In addition, the proposed SmPC for Benepali states that there is an increased background risk for lymphoma and leukaemia in RA patients with long-standing, highly active, inflammatory disease. Studies have shown that patients with RA have an approximately 2-fold increased risk of lymphoma and leukaemia, a 20% to 50% increased risk of respiratory tract cancer, and a 70% increased risk of non-melanoma skin cancers, but a decreased risk for breast and colorectal cancer. The increase in lymphoma risk is limited to those RA patients who have long-standing and very severe disease.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4 and 4.8 PL Sections 2 and 4 Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Registry participation See section II.C of this summary for an overview of the post-authorisation development plan.

Serious and opportunistic infections (including tuberculosis, Legionella, Listeria, parasitic infection)	
Evidence for linking the risk to the medicine	Study SB4-G31-RA; referenced scientific publications.
Risk factors and risk groups	The patients who are on concomitant immunosuppressive therapy, in addition to their underlying disease, can be predisposed to infection.
Risk minimisation measures	Routine risk minimisation measures SmPC section 4.3, 4.4, and 4.8 PL Sections 2 and 4 Additional risk minimisation measures Patient cards are provided to etanercept prescribing physicians for distribution to patients receiving etanercept. This card provides important safety information for patients, including information relating to infections
Additional pharmacovigilance activities	Additional pharmacovigilance activities Registry participation See section II.C of this summary for an overview of the post-authorisation development plan.

Demyelinating disorders	
Evidence for linking the risk to the medicine	Study SB4-G31-RA; proposed SmPC for Benepali, Section 4.4 'Special warnings and precautions for use'; referenced scientific publications.
Risk factors and risk groups	In RA, the primary autoimmune condition may be a contributing factor to the development of demyelinating disorders, other inflammatory rheumatic disorders, particularly SpAs, are not classically associated with immune neurological disorders. Potential risk factors for central demyelinating disorders include vitamin D deficiency and certain childhood infections including Epstein-Barr virus.
Risk minimisation measures	Routine risk minimisation measures SmPC section 4.4 and 4.8 PL Sections 2 and 4 Additional risk minimisation measures None
Additional pharmacovigilance activities	Additional pharmacovigilance activities Registry participation See section II.C of this summary for an overview of the post-authorisation development plan.

Aplastic anaemia and pancytopenia	
Evidence for linking the risk to the medicine	Study SB4-G31-RA; proposed SmPC for Benepali, Section 4.4 'Special warnings and precautions for use'; referenced scientific publications.
Risk factors and risk groups	Although no high risk group has been identified, caution should be exercised in subjects being treated with etanercept who have a previous history of significant haematological abnormalities.
Risk minimisation measures	Routine risk minimisation measures SmPC section 4.4 and 4.8 PL Sections 2 and 4 Additional risk minimisation measures None
Additional pharmacovigilance activities	Additional pharmacovigilance activities Registry participation See section II.C of this summary for an overview of the post-authorisation development plan.

CHF in adult subjects	
Evidence for linking the risk to the medicine	Study SB4-G31-RA; proposed SmPC for Benepali, Section 4.4 'Special warnings and precautions for use'; referenced scientific publications.
Risk factors and risk groups	Subjects with known ischaemic heart disease, especially those with a previous history of CHF
Risk minimisation measures	Routine risk minimisation measures SmPC section 4.4 and 4.8 PL Sections 2 and 4 Additional risk minimisation measures Patient cards are provided to etanercept prescribing physicians for distribution to patients receiving etanercept. This card provides important safety information for patients, including information relating to congestive heart failure
Additional pharmacovigilance activities	Additional pharmacovigilance activities Registry participation, See section II.C of this summary for an overview of the post-authorisation development plan.

II.B.2 Important potential risks

Encephalitis/leukoencephalomyelitis	
Evidence for linking the risk to the medicine	Study SB4-G31-RA.
Risk factors and risk groups	Subjects on concomitant immunosuppressive therapy, or with medical conditions that cause immunosuppression that, in addition to their underlying disease, could predispose them to infections.
Risk minimisation measures	Routine risk minimisation measures None Additional risk minimisation measures None
Additional pharmacovigilance activities	Additional pharmacovigilance activities Registry participation See section II.C of this summary for an overview of the post-authorisation development plan.

Progressive multifocal leukoencephalopathy	
Evidence for linking the risk to the medicine	Study SB4-G31-RA; referenced scientific publications.
Risk factors and risk groups	Patients on concomitant immunosuppressive therapy that, along with their underlying disease, could predispose them to PML.
Risk minimisation measures	Routine risk minimisation measures None Additional risk minimisation measures None
Additional pharmacovigilance activities	Additional pharmacovigilance activities Registry participation See section II.C of this summary for an overview of the post-authorisation development plan.

Impaired growth and development in juvenile subjects	
Evidence for linking the risk to the medicine	Referenced scientific publications
Risk factors and risk groups	There are currently no known risk groups or risk factors in patients following the administration of etanercept for events in growth and development.
Risk minimisation measures	Routine risk minimisation measures None Additional risk minimisation measures None
Additional pharmacovigilance activities	Additional pharmacovigilance activities None

Acute ischemic CV events in adult subjects	
Evidence for linking the risk to the medicine	Study SB4-G31-RA; referenced scientific publications.
Risk factors and risk groups	Currently, there are no known risk groups or risk factors for the development of acute ischemic cardiovascular events with etanercept treatment.
Risk minimisation measures	Routine risk minimisation measures None Additional risk minimisation measures None
Additional pharmacovigilance activities	Additional pharmacovigilance activities Registry participation See section II.C of this summary for an overview of the post-authorisation development plan.

II.B.3 Missing information

Not applicable

II.C Post-authorisation development plan

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

There are no studies which are conditions of the marketing authorisation or specific obligation of Benepali.

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

BSRBR-RA

Purpose of the study: An established nationwide register for patients with rheumatological disorders treated with biologic agents. The register is designed as a national prospective study whose primary purpose is to assess long-term toxicity from the use of these agents in routine practice.

RABBIT

Purpose of the study: A prospective, observational cohort study whose objectives are to evaluate the long-term effectiveness, safety, and costs associated with tumour necrosis factor-inhibitor therapies in the treatment of RA and to compare this to a cohort of RA patients who are treated with non-biologic DMARDs.

ARTIS

Purpose of the study: A national prospective, observational, uncontrolled cohort study whose objectives are to evaluate the risk of selected AEs in RA, juvenile idiopathic arthritis, and other rheumatic disease patients treated with etanercept.

BADBIR

Purpose of the study: A nationwide registry which seeks to assess the long-term safety of biologic treatments for psoriasis. Recommended by NICE that all patients in the UK receiving new therapies for psoriasis be registered in BADBIR.