Summary of risk management plan for Enbrel (etanercept)

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

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

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

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

I. The Medicine and What It Is Used For

ENBREL 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 list of indications). It contains etanercept as the active substance and it is given by injection.

Further information about the evaluation of ENBREL's benefits can be found in ENBREL'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/enbrel.

II. Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of ENBREL, together with measures to minimise such risks and the proposed studies for learning more about ENBREL'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 the case of ENBREL, 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*.

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

II.A. List of Important Risks and Missing Information

Important risks of ENBREL 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 ENBREL. 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).

Table 1. List of important risks and missing information

Important identified risks	Malignancy (including lymphoma and leukaemia)
	Serious and Opportunistic Infections (including tuberculosis, *Legionella*, *Listeria*, and parasitic infections)
	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 Ischaemic Cardiovascular Events in Adults Subjects
Missing information	Immunogenicity Profile and Related Clinical Outcomes of Etanercept Manufactured using the SFPHC Process in a Real-life Post-marketing Setting

SFPHC = serum free process high capacity

II.B. Summary of Important Risks

Table 2. Important Identified Risk – Malignancy (including lymphoma and leukaemia)

Evidence for linking the risk to the medicine	Clinical trial and post-marketing data.
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.

Table 2. Important Identified Risk – Malignancy (including lymphoma and leukaemia)

Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4 Special warnings and precautions SmPC section 4.8 Undesirable effects PL Sections 2 and 4 Additional risk minimisation measures: None proposed.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None proposed. See Section II.C of this summary for an overview of the post-authorisation development plan.

PL = package leaflet; PsO = psoriasis; RA = rheumatoid arthritis; SmPC = summary of product characteristics

Table 3. Important Identified Risk – Serious and Opportunistic Infections (Including Tuberculosis, *Legionella, Listeria,* and Parasitic Infections)

Evidence for linking the risk to the medicine	Clinical trial and post-marketing data.
Risk factors and risk groups	Subjects on concomitant immunosuppressive therapy, in addition to their underlying disease, could be predisposed to infections. Treatment of moderate to severe PsO has typically involved conventional systemic therapies such as MTX, cyclosporine, and oral retinoids, or phototherapy, which may increase the incidence of infections. Studies have shown that cyclosporine can be associated with influenza-like symptoms (9.9%) and upper respiratory tract infections (7.7%) when administered to subjects with PsO.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.3 Contraindications SmPC Section 4.4 Special warnings and precautions SmPC Section 4.8 Undesirable effects 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: None proposed. See Section II.C of this summary for an overview of the post-authorisation development plan.

MTX = methotrexate; PL = package leaflet; PsO = psoriasis; SmPC = summary of product characteristics

Table 4. Important Identified Risk – Demyelinating Disorders

Evidence for linking the risk to the medicine	Clinical trial and post-marketing data.
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 Special warnings and precautions SmPC Section 4.8 Undesirable effects PL Section 2 and 4 Additional risk minimisation measures: None proposed.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None proposed. See Section II.C of this summary for an overview of the post-authorisation development plan.

PL = package leaflet; RA = rheumatoid arthritis; SmPC = summary of product characteristics; SpA = spondyloarthritis

Table 5. Important Identified Risk – Aplastic Anaemia and Pancytopenia

Evidence for linking the risk to the medicine	Clinical trial and post-marketing data.
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 Special warnings and precautions SmPC Section 4.8 Undesirable effects PL Sections 2 and 4 Additional risk minimisation measures: None proposed.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None proposed. See Section II.C of this summary for an overview of the post-authorisation development plan.

PL = package leaflet; SmPC = summary of product characteristics

Table 6. Important Identified Risk – Congestive Heart Failure in Adult Subjects

Evidence for linking the risk to the medicine	Clinical trial and post-marketing data.
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 Special warnings and precautions SmPC Section 4.8 Undesirable effects 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: None proposed. See Section II.C of this summary for an overview of the post-authorisation development plan.

CHF = congestive heart failure; PL = package leaflet; SmPC = summary of product characteristics

Table 7. Important Potential Risk – Encephalitis/Leukoencephalomyelitis

Evidence for linking the risk to the medicine	Clinical trial and post-marketing data.
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 proposed. Additional risk minimisation measures: None proposed.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None proposed. See Section II.C of this summary for an overview of the post-authorisation development plan.

Table 8. Important Potential Risk – Progressive Multifocal Leukoencephalopathy

Evidence for linking the risk to the medicine	Clinical trial and post-marketing data.
Risk factors and risk groups	Subjects on concomitant immunosuppressive therapy that, in addition to their underlying disease, could predispose them to PML.
Risk minimisation measures	Routine risk minimisation measures: None proposed. Additional risk minimisation measures: None proposed.

Table 8. Important Potential Risk – Progressive Multifocal Leukoencephalopathy

Additional pharmacovigilance activities	Additional pharmacovigilance activities: None proposed. See Section II.C of this summary for an overview of the post-authorisation development plan.

PML = progressive multifocal leukoencephalopathy

Table 9. Important Potential Risk – Impaired Growth and Development in Juvenile Subjects

Evidence for linking the risk to the medicine	Clinical trial and post-marketing data.
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 proposed. Additional risk minimisation measures: None proposed.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None proposed. See Section II.C of this summary for an overview of the post-authorisation development plan.

Table 10. Important Potential Risk – Acute Ischaemic CV Events in Adult Subjects

Evidence for linking the risk to the medicine	Clinical and post-marketing data.
Risk factors and risk groups	There are no known risk factors or subject groups at risk for the development of ischaemic cardiovascular events with treatment with etanercept.
Risk minimisation measures	Routine risk minimisation measures: None proposed. Additional risk minimisation measures: None proposed.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None proposed. See Section II.C of this summary for an overview of the post-authorisation development plan.

CV = cardiovascular

Table 11. Missing Information – Immunogenicity Profile and Related Clinical Outcomes of Etanercept Manufactured using the SFPHC Process in a Real-life Post-marketing Setting

Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4 Special warnings and precautions A sticky/peel-off traceability label on the other packaging 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 instructions to record the brand name and batch number of the medication.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: BSRBR See section II.C of this summary for an overview of the post-authorisation development plan.

BSRBR = British Society of Rheumatology Biologics Register; SFPHC = serum free process high capacity; SmPC = summary of product characteristics

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 etanercept.

II.C.2. Other Studies in Post-Authorisation Development Plan

BSRBR

Purpose of the study: This is a large prospective observational study that obtains data from routine clinical practice and whose objective is to evaluate any excess risk in the occurrence of various adverse events in patients with RA, AS, and PsA after allowing for confounding factors particularly of disease severity and concomitant rheumatic disease therapy. In addition, a long-term pharmacoepidemiological surveillance comparing the safety profile of etanercept before and after 3 years of introduction of drug product manufactured from a new high capacity drug substance manufacturing process will be conducted using data from BSRBR. The safety concern to be monitored is the immunogenicity profile and related clinical outcomes of etanercept manufactured using the SFPHC process in a real-life post-marketing setting.