Summary of the risk management plan for Erelzi (etanercept)

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

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

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

I. The medicine and what it is used for

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

Further information about the evaluation of Erelzi's benefits can be found in Erelzi'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/erelzi.

II. Risks associated with the medicine and activities to minimize or further characterize the risks

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

Measures to minimize 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 minimize its risks.

Together, these measures constitute *routine risk minimization* measures.

In the case of Erelzi, these measures are supplemented with *additional risk minimization measures* mentioned under relevant important risks, below.

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 Erelzi is not yet available, it is listed under 'missing information' below.

II.A: List of important risks and missing information

Important risks of Erelzi are risks that need special risk management activities to further investigate or minimize 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 Erelzi. 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

List of important risks and missing information	
Important identified risks –	Malignancy (including lymphoma and leukemia)
	Serious and opportunistic infections (including tuberculosis, Legionella, Listeria, parasitic infection)
	Demyelinating disorders
	Aplastic anemia 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	None

II B: Summary of important risks

Important identified risk: Malignancies (including lymphoma and leukemia)

Evidence for linking the risk to the medicine	Clinical trials 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.
Risk minimization measures	Routine risk minimization measures: SmPC sections 4.4 and 4.8 PL sections 2 and 4 Legal status: Prescription only medicine Additional risk minimization measures: None

Important identified risk (all indications): Serious and opportunistic infections (including tuberculosis, Legionella, Listeria, and parasitic infection)

Evidence for linking the risk to the medicine	Clinical trials and postmarketing data
Risk factors and risk groups	Serious infections were reported in both adult and pediatric subjects and across all indications. Patients concomitantly treated with other immunosuppressant medicines are at increased risk.
Risk minimization measures	Routine risk minimization measures: SmPC sections 4.3, 4.4, 4.5, 4.6 and 4.8 PL sections 2 and 4 Legal status: Prescription only medicine Additional risk minimization measures: Patient card.

Important identified risk: Demyelinating disorders

Evidence for linking the risk to the medicine	Clinical trials and postmarketing data
Risk factors and risk groups	Potential risk factors may include subjects with pre-existing or recent-onset demyelinating disorders.
Risk minimization measures	Routine risk minimization measures: SmPC sections 4.4 and 4.8 PL sections 2 and 4 Legal status: Prescription only medicine Additional risk minimization measures: None

Important identified risk: Aplastic anemia and pancytopenia

Evidence for linking the risk to the medicine	Clinical trials and postmarketing 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 hematological abnormalities.
Risk minimization measures	Routine risk minimization measures: SmPC sections 4.4 and 4.8 PL section 2 and 4 Legal status: Prescription only medicine Additional risk minimization measures: None

Important identified risk: Congestive heart failure in adult subjects

Evidence for linking the risk to the medicine	Clinical trial and postmarketing data
Risk factors and risk groups	Subjects with known ischaemic heart disease, especially those with a previous history of CHF
Risk minimization measures	Routine risk minimization measures: SmPC sections 4.4 and 4.8 PL sections 2 and 4 Legal status: Prescription only medicine Additional risk minimization measures: Patient card

Important potential risk: Encephalitis/leukoencephalomyelitis

Evidence for linking the risk to the medicine	Clinical trials and postmarketing 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 minimization measures	Routine risk minimization measures: None Legal status: Prescription only medicine Additional risk minimization measures: None

Important potential risk: Progressive multifocal leukoencephalopathy

Evidence for linking the risk to the medicine	Clinical trials and postmarketing data
Risk factors and risk groups	Subjects on concomitant immunosuppressive therapy that, in addition to their underlying disease, could predispose them to PML.
Risk minimization measures	Routine risk minimization measures: None

	Legal status: Prescription only medicine Additional risk minimization measures: None

Important potential risk: Impaired growth and development in juvenile subjects

Evidence for linking the risk to the medicine	Clinical trials and postmarketing data A potential effect of etanercept on growth and development is not known. Giannini et al (2010) reported that etanercept treatment, with or without methotrexate, may rather contribute to restoration of normal growth in children with juvenile idiopathic arthritis.
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 minimization measures	Routine risk minimization measures: None Legal status: Prescription only medicine Additional risk minimization measures: None

Important potential risk: Acute ischemic cardiovascular events in adult subjects

Evidence for linking the risk to the medicine	Clinical trials and postmarketing data There is no strong evidence that TNF-α inhibitors including etanercept are associated with an increased risk of acute ischemic cardiovascular events. A meta-analysis by Roubille et al (2015) reported a reduced risk of all cardiovascular events in rheumatoid arthritis patients with TNFα inhibitors (risk ratio (RR), 0.70; 95% CI 0.54-0.90) and methotrexate (RR, 0.72; 95% CI 0.57-0.91).
Risk factors and risk groups	There are no known risk factors or subject groups at risk for the development of ischemic cardiovascular events with treatment with etanercept.
Risk minimization measures	Routine risk minimization measures: None Legal status: Prescription only medicine Additional risk minimization measures: None

II C: Post-authorization development plan

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

There are no studies which are conditions of the marketing authorization or specific obligation of Erelzi.

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

There are no studies required for Erelzi.