Based on EU RMP version 2.1
2. September 2021

Public Risk Management Plan (RMP) Summary

NEPEXTO® (Etanercept)

Etanercept injection 50mg/ml and 25mg/0.5ml

(prefilled syringe and prefilled pen)

Disclaimer:

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 minimise them.

The RMP summary of **NEPEXTO®** 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 NEPEXTO® in Switzerland is the "Arzneimittelinformation / Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. Mylan Pharma GmbH is fully responsible for the accuracy and correctness of the content of the published summary RMP of NEPEXTO®.

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2. September 2021

Summary of risk management plan for Nepexto® (Etanercept)

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

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

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

I. The medicine and what it is used for

Nepexto is authorised for

1. Treatment of rheumatoid arthritis (a disease-causing inflammation of the joints) in adults, used with another medicine, methotrexate, or alone;
2. Treatment of certain forms of juvenile idiopathic arthritis (diseases causing inflammation in the joints, with first appearance in childhood or adolescence);
3. Treatment of plaque psoriasis (a disease causing red, scaly patches on the skin) in adults and children;
4. Treatment of psoriatic arthritis (psoriasis with inflammation of the joints) in adults and adolescents;
5. Treatment of ankylosing spondylitis (a disease-causing inflammation of the joints of the spine) in adults;
6. Treatment of axial spondyloarthritis (a chronic inflammatory disease of the spine) in adults when there are no abnormalities seen on x-ray.

It contains etanercept as the active substance and it is administered subcutaneously.

Further information about the evaluation of Nepexto's benefits can be found in Nepexto's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's https://www.ema.europa.eu/en/medicines/human/EPAR/nepexto.

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

Important risks of Nepexto, together with measures to minimise such risks are outlined below.

Measures to minimise the risks identified for medicinal products include:

- 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 Nepexto, these measures are supplemented with additional risk minimisation 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*.

II.A List of important risks and missing information

Important risks of Nepexto® are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely 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 Nepexto®. 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).

Summary of safety concerns

List of important risks and missing information	
Important identified risks - all indications	• Malignancy (including lymphoma and leukemia) • Serious and opportunistic infections (including tuberculosis, Legionella, Listeria and parasitic infections)

List of important risks and missing information	
	• Demyelinating disorders • Aplastic anaemia and pancytopenia • Congestive heart failure [CHF] in adult subjects
Important potential risks - all indications	• Encephalitis/ leukoencephalomyelitis • Progressive multifocal leukoencephalopathy [PML] • Impaired growth and development of juvenile subjects • Acute ischaemic cardiovascular [CV] events in adult subjects
Missing information	None

II.B Summary of important risks

Important Identified Risk 1: Malignancy (including lymphoma and leukemia)	
Evidence for linking the risk to the medicine	Reports of various malignancies (including breast and lung carcinoma and lymphoma) have been received in the post-marketing period. Based on current knowledge, a possible risk for the development of lymphomas, leukaemia or other haematopoietic or solid malignancies in patients treated with a TNF-antagonist cannot be excluded. Melanoma and non-melanoma skin cancer (NMSC) have been reported in patients treated with TNF-antagonists, including etanercept. Post-marketing cases of Merkel cell carcinoma have been reported very infrequently in patients treated with etanercept. Analysis of the risk attributable to etanercept of relatively rare events like malignancy can be assessed by comparing the rates observed in the two phase 3 studies to those of an appropriate historical population. The observed number of extracutaneous cancers in the etanercept psoriasis database (10 extracutaneous malignancies/1038.7 patient-years = 1.0 per 100 patient-years) is not significantly different from the expected rate based on calculations using the general population database from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database (0.5 per 100 patient-years; 95% confidence interval [CI] = 0.2-1.1). The SEER database does not include non-melanoma skin cancers.
Risk factors and risk groups	Patients with RA have a 10 % increase in overall malignancy risk compared with the general population. Furthermore, the standardized incidence ratio (SIR) estimates for patients with RA continued to show an increased risk of lymphoma and lung cancer as previously observed. Overall, SIR estimates for colorectal and breast cancers continued to show a decrease in risk, whereas cervical cancer, prostate cancer and melanoma appeared to show

	no consistent trend in risk among patients with RA compared with the general population. Several studies have confirmed that the risk of malignancy in psoriasis patients exceeds that in the normal population, and standardised incidence ratios of 1.78 (95% CI 1.32-2.40), 1.3 (95% CI 1.2-1.4), 1.37 (95% CI 1.28-1.47), and 1.35 (95% CI 1.22-1.49) have been reported.
Risk minimisation measures	Routine risk minimisation measures *SmPC section 4.4 and 4.8* *PL section 2 and 4* Legal status: prescription only medicine Additional risk minimisation measures *None*
Additional pharmacovigilance activities	German Biologics Register – Rheumatoid Arthritis (RABBIT) See section II.C of this summary for an overview of the post-authorisation development plan.

Important Identified Risk 2: Serious and opportunistic infections (including tuberculosis, Legionella, Listeria and parasitic infections)	
Evidence for linking the risk to the medicine	Rates of infections (the most frequently reported adverse event) were related to the duration of treatment. The most serious infections that have been reported with medicinal products containing etanercept are invasive fungal infections, listeriosis and legionellosis, active tuberculosis, including miliary tuberculosis and tuberculosis with extra-pulmonary location. Upper respiratory tract infections were the most commonly reported type of infection. Increased cough and respiratory disorders ("colds") were found to be significantly more frequent ($p<0.05$) in the high dose group compared to placebo and to the mid dose group. A trend ($p< 0.10$) toward association of fever with etanercept treatment overall and with high dose treatment as compared to placebo was noted. The majority of fevers were associated with infections or other inflammatory conditions. In the sepsis clinical trial, 108 patients with documented sepsis were treated with etanercept and 33 patients received placebo. In this study, the patient group was severely immuno-compromised. A higher mortality was observed in the etanercept -treated than in the placebo-treated group when the infection was caused by gram-positive or unknown microbes, and the mortality rate was raised in the groups treated with high doses of etanercept. The increased mortality observed with increasing dose could not be explained by imbalances at enrolment. Mortality was not related to an identifiable direct toxicity of etanercept.
Risk factors and risk groups	Standard-dose and high-dose biological drugs (with or without traditional disease-modifying anti-rheumatic drugs [DMARDs]) have been shown to be associated with a statistically significant increase in serious infections in methotrexate-naïve rheumatoid arthritis patients compared with traditional DMARDs; the absolute risk increase of serious infections with biologic therapy was identified as 6 per 1000 for standard-dose biologic and 17 per 1000 for high-dose biologic therapy. Patient on concomitant treatment with other immunosuppressant are at additional risk.
Risk minimisation measures	Routine risk minimisation measures *SmPC sections 4.3, 4.4 and 4.8* *PL section 2 and 4* Legal status: prescription only medicine Additional risk minimisation measures *Patient Card*

Additional pharmacovigilance activities	German Biologics Register – Rheumatoid Arthritis (RABBIT) See section II.C of this summary for an overview of the post-authorisation development plan.

Important Identified Risk 3: Demyelinating disorders	
Evidence for linking the risk to the medicine	There have been rare reports of CNS demyelinating disorders in patients treated with etanercept. Additionally, there have been very rare reports of peripheral demyelinating polyneuropathies (including Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, demyelinating polyneuropathy, and multifocal motor neuropathy). Although no clinical trials have been performed evaluating etanercept therapy in patients with multiple sclerosis, clinical trials of other TNF antagonists in patients with multiple sclerosis have shown increases in disease activity.
Risk factors and risk groups	Patients with pre-existing or recent onset of demyelinating disease, or to those who are considered to have an increased risk of developing demyelinating disease. Risk factors for GBS include male sex, prior infection (e.g. Campylobacter jejuni, Epstein Barr virus, cytomegalovirus, mycoplasma, HIV, and more recently Zika virus, vaccines, malignancies (e.g. lymphomas, especially Hodgkin's disease).
Risk minimisation measures	Routine risk minimisation measures *SmPC sections 4.3, 4.4 and 4.8* *PL section 2 and 4* Legal status: prescription only medicine Additional risk minimisation measures *None*
Additional pharmacovigilance activities	German Biologics Register – Rheumatoid Arthritis (RABBIT) See section II.C of this summary for an overview of the post-authorisation development plan.

Important Identified Risk 4: Aplastic anaemia and pancytopenia	
Evidence for linking the risk to the medicine	Rare cases of pancytopenia and very rare cases of aplastic anaemia, some with fatal outcome, have been reported in patients treated with etanercept
Risk factors and risk groups	Currently available data could not identify specific risk factor for risk group.

Risk minimisation measures	Routine risk minimisation measures *SmPC sections 4.3, 4.4 and 4.8* *PL section 2 and 4* Legal status: prescription only medicine Additional risk minimisation measures *None*
Additional pharmacovigilance activities	German Biologics Register – Rheumatoid Arthritis (RABBIT) See section II.C of this summary for an overview of the post-authorisation development plan.

Important Identified Risk 5: Congestive heart failure [CHF] in adult subjects	
Evidence for linking the risk to the medicine	There have been rare (< 0.1%) reports of new onset CHF, including CHF in patients without known pre-existing cardiovascular disease. Some of these patients have been under 50 years of age.
Risk factors and risk groups	Currently available data could not identify specific risk factor for risk group other than the patients having CHF.
Risk minimisation measures	Routine risk minimisation measures *SmPC sections 4.3, 4.4 and 4.8* *PL section 2 and 4* Legal status: prescription only medicine Additional risk minimisation measures *Patient Card*
Additional pharmacovigilance activities	German Biologics Register – Rheumatoid Arthritis (RABBIT) See section II.C of this summary for an overview of the post-authorisation development plan.

Important potential risks

Important Identified Risk 1: Encephalitis/ leukoencephalomyelitis	
Evidence for linking the risk to the medicine	Currently available data is not sufficient. The impact of long-term treatment with etanercept on the development of immune mediated reaction is unknown.
Risk factors and risk groups	Currently available data could not identify specific risk factor for risk group.
Risk minimisation measures	Currently available data do not support the need for risk minimization.

Additional pharmacovigilance activities	German Biologics Register – Rheumatoid Arthritis (RABBIT) See section II.C of this summary for an overview of the post-authorisation development plan.

Important Identified Risk 2: Progressive multifocal leukoencephalopathy [PML]	
Evidence for linking the risk to the medicine	Currently available data is not sufficient.
Risk factors and risk groups	PML primarily affects individuals with chronically and severely suppressed immune systems and is associated primarily with HIV patients, haematological malignancies, or relapsing–remitting multiple sclerosis patients treated with natalizumab. PML is also associated with other conditions such as organ transplantation, solid malignancies, sarcoidosis, autoimmune disorders (e.g. lupus, RA), and congenital immune deficiencies; these populations individually contribute a relatively small number of cases and together account for less than 10% of all reported PML cases.
Risk minimisation measures	Currently available data do not support the need for risk minimization.
Additional pharmacovigilance activities	German Biologics Register – Rheumatoid Arthritis (RABBIT) See section II.C of this summary for an overview of the post-authorisation development plan.

Important Identified Risk 3: Impaired growth and development of juvenile subjects	
Evidence for linking the risk to the medicine	Currently available data is not sufficient.
Risk factors and risk groups	Currently available data could not identify specific risk factor for risk group.
Risk minimisation measures	Currently available data do not support the need for risk minimization.

Important Identified Risk 4: Acute ischaemic cardiovascular [CV] events in adult subjects	
Evidence for linking the risk to the medicine	Currently available data is not sufficient.
Risk factors and risk groups	Currently available data could not identify specific risk factor for risk group

Risk minimisation measures	Currently available data do not support the need for risk minimization.
Additional pharmacovigilance activities	German Biologics Register – Rheumatoid Arthritis (RABBIT) See section II.C of this summary for an overview of the post-authorisation development plan.

II.C Post-authorisation development plan

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

There are no studies which are condition to marketing authorisation or specific obligation of Nepexto.

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

German Biologics Register – Rheumatoid Arthritis (RABBIT): Safety surveillance of Nepexto (etanercept) using the rheumatoid arthritis RABBIT registry in Germany: long term, prospective, observational study.

Purpose of the study:

In order to characterise the safety profile of the etanercept biosimilar formulation Nepexto, and to describe the effectiveness and response to the treatment in rheumatoid arthritis (RA) patients in a real-life environment, this observational post-authorisation safety study is planned, using already existing data from the *Rheumatoide Arthritis: Beobachtung der Biologika-Therapie* registry (RABBIT) in Germany. As primary objective, this registry will address the long-term safety profile of Nepexto in RA patients in a real-life environment. As secondary objective, this registry is to describe the long-term effectiveness and response to treatment in patients using Nepexto in a real-life environment.