Summary of the risk management plan for Tyruko (natalizumab)

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

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

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

I. The medicine and what it is used for

Tyruko is authorised for use as a single disease modifying therapy (DMT) in adult patients with highly active relapsing remitting multiple sclerosis (RRMS) (see SmPC for the full indication). It contains natalizumab as the active substance and it is given by intravenous infusion.

Further information about the evaluation of Tyruko's benefits can be found in Tyruko'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/tyruko

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

Important risks of Tyruko together with measures to minimize such risks and the proposed studies for learning more about these 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 Tyruko, 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*.

II.A: List of important risks and missing information

Important risks of Tyruko 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 Tyruko. 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	Progressive multifocal leukoencephalopathy (PML) Serious herpes infections
Important potential risks	Malignancies
Missing information	PML risk following switch from disease modifying therapies with immunosuppressant effect

II B: Summary of important risks

Important identified risk: Progressive multifocal leukoencephalopathy (PML)	
Evidence for linking the risk to the medicine	Use of natalizumab has been associated with the uncommon event of PML, which may be fatal or result in severe disability. PML has been classified as an important identified risk for Tyruko, consistent with the reference product, Tysabri.
Risk factors and risk groups	The following risk factors are associated with an increased risk of PML: • The presence of anti-JCV antibodies. • Treatment duration, especially beyond 2 years. After 2 years all patients should be re-informed about the risk of PML with the medicinal product.

	• Immunosuppressant use prior to receiving the medicinal product. Patients who are anti-JCV antibody positive are at an increased risk of developing PML compared to patients who are anti-JCV antibody negative. Patients who have all three risk factors for PML (i.e., are anti-JCV antibody positive and have received more than 2 years of therapy with this medicinal product and have received prior immunosuppressant therapy) have a significantly higher risk of PML. In anti-JCV antibody positive natalizumab treated patients who have not used prior immunosuppressants the level of anti-JCV antibody response is associated with the level of risk for PML. Anti-JCV antibody negative patients may still be at risk of PML for reasons such as a new JCV infection, fluctuating antibody status or a false negative test result. Patients who test as positive for anti-JCV antibodies at any time should be considered to be at an increased risk for developing PML, independent from any prior or subsequent antibody test results.
Risk minimization measures	Routine risk minimization measures: Information in SmPC Sections 4.2, 4.3, 4.4, 4.8, and 5.1; and PL Sections 2 and 4 Legal status: Restricted medical prescription Additional risk minimization measures: Educational tools for HCPs (Physician Information and Management Guideline) Educational tools for patients/carers (patient alert card, treatment initiation form, treatment continuation form, and treatment discontinuation form)

Important identified risk: Serious herpes infections

Evidence for linking the risk to the medicine	Serious herpes infections has been classified as an important identified risk for Tyruko, consistent with the reference product, Tysabri.
Risk factors and risk groups	None identified for natalizumab.
Risk minimization measures	Routine risk minimization measures: Information in SmPC Sections 4.3, 4.4, 4.8; and PL Sections 2 and 4 Legal status: Restricted medical prescription

Important potential risk: Malignancies	
Evidence for linking the risk to the medicine	Malignancies have been classified as an important potential risk for Tyruko, consistent with the reference product, Tysabri. Malignancies were included as an important potential risk for Tysabri based on the class of product and on the scientific literature. There is currently no evidence to suggest an increased risk for malignancy associated with long-term natalizumab therapy, however, observation over longer treatment periods is required before any effect of natalizumab on malignancies can be excluded.
Risk factors and risk groups	No risk groups or risk factors have been identified.
Risk minimization measures	Routine risk minimization measures: Information in SmPC Sections 4.3 and 4.8; and PL Section 2 Legal status: Restricted medical prescription

Missing information: PML risk following switch from disease modifying therapies with immunosuppressant effect	
Risk minimization measures	Routine risk minimization measures: Information in SmPC Section 4.4 and PL Section 2. Legal status: Restricted medical prescription

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 Tyruko.

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

There are no studies required for Tyruko.