Summary of Risk Management Plan (RMP)

Tysabri™ (Natalizumab)

Biogen Switzerland AG

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Summary of the Risk Management Plan (RMP) for Tysabri™ (Natalizumab)

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 Tysabri™ 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 Tysabri™ in Switzerland is the "Arzneimittelinformation / Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. Biogen Switzerland AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of Tysabri™.

Summary of risk management plan for Tysabri (natalizumab)

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

The Tysabri Summary of Product Characteristics (SmPC) and its Package Leaflet (PL) give essential information to healthcare professionals and patients on how Tysabri should be used.

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

Important new safety concerns or changes to the current described safety concerns will be included in updates of the RMP for Tysabri.

VI: 1 The medicine and what it is used for

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

Further information about the evaluation of the benefits of Tysabri can be found in the EPAR for Tysabri, including in its plain-language summary, available on the EMA (European Medical Agency) website.

VI: 2 Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Tysabri, together with measures to minimise such risks and the proposed studies for learning more about Tysabri'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, respectively;
- Important advice on the medicine’s packaging;
- The authorised pack size — the amount of medicine in a pack is chosen to ensure that the medicine is used correctly; and
- 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 Tysabri, 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 Periodic Safety Update Report (PSUR) assessments 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 Tysabri is not yet available, it is listed under 'missing information' below.

VI: 2.1 List of important risks and missing information

Important risks of Tysabri 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 categorised as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Tysabri. 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 needs to be collected (e.g. on the long- term use of the medicine):

List of important risks and areas of missing information	
Important identified risks	• Progressive Multifocal Leukoencephalopathy (PML) • Serious herpes infections
Important potential risks	• Malignancies
Areas of missing information	• PML risk following switch from disease modifying therapies with immunosuppressant effect • Immunogenicity potential of subcutaneously administered Tysabri (anti-natalizumab antibody formation resulting in a potential adverse clinical consequence of serious hypersensitivity reactions including anaphylaxis)

VI: 2.2 Summary of important risks

This section presents a summary of important identified risks, important potential risks and missing information.

Important Identified Risks	
Progressive multifocal leukoencephalopathy (PML)	
Evidence for linking the risk to the medicine	It is noted that all data available to characterise PML risk are from the IV route of administration. Considering the similar pharmacodynamic profiles, the same PML risk and relevant risk factors are also assumed for the different routes of administration (eg, SC). PML was reported in two patients in pre-authorization multiple sclerosis (MS) trials after about 2 years of combination treatment with

Important Identified Risks	
	natalizumab and beta- IFN 1a (AVONEX®). A third case was reported in a patient from the Crohn's disease clinical trials, who had terminated use of immunosuppressants 2 to 3 months prior to starting natalizumab monotherapy. In the post-marketing setting, Biogen utilizes a framework that uses standardized criteria and case definitions to differentiate and classify reported cases of PML by levels of diagnostic certainty. This objective adjudication process was developed with external PML expert input and has been used to evaluate PML case reports for natalizumab for several years. PML case definitions (which categorize cases into Level 1 to Level 5) allow classification of cases based on various levels of diagnostic certainty, ranging from the highest to lowest. It outlines specific criteria for ruled-out (Level 5), includes a category for cases with insufficient data despite exhaustive due diligence (Level 4), as well as categories for high and low suspect cases (Levels 2 and 3, respectively). Following this adjudication process, confirmed PML cases (Level 1) have been identified in association with natalizumab use. Consequently, PML was added as a listed adverse drug reaction (ADR) in Section 4.8 (Undesirable effects) of the natalizumab SmPC, and wording relating to the detection and management of PML was implemented in Section 4.4 (Special warnings and precautions for use).
Risk factors and risk groups	PML can only occur in the presence of a John Cunningham virus (JCV) infection, with studies indicating that approximately 60-70% of MS patients were seropositive when screened for anti-JCV antibody. • The following risk factors are associated with an increased risk of PML in natalizumab-treated patients: The presence of anti-JCV antibodies • Treatment duration; especially beyond 2 years • Immunosuppressant prior to receiving Tysabri Patients who have all three risk factors for PML (i.e., are anti-JCV antibody positive and have received more than 2 years of natalizumab therapy and have received prior immunosuppressant therapy) have a significantly higher risk of PML. In anti-JCV antibody positive Tysabri treated patients who have not used prior immunosuppressants the level of anti-JCV antibody response (index) is associated with the level of risk for PML (i.e., the risk is greater in those with a high antibody index compared to those with a low index). Currently available evidence suggests that the risk of PML is low at an index equal to or below 0.9 and increases substantially above 1.5 for patients who have been on treatment with Tysabri for longer than two years. 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.

Important Identified Risks	
	Patients who test anti-JCV antibody positive at any time should be considered to be at an increased risk for developing PML, independent from any prior or subsequent antibody test results. Using the three risk factors (JCV antibody status, prior immunosuppressant use and duration of Tysabri therapy), and patients with high anti-JCV antibody index who have received more than 2 years of Tysabri therapy and without prior history of immunosuppressant therapy, subgroups of patients with distinctly lower and higher risk for PML can be identified. Consequently, an algorithm containing these risk factors and the associated PML risk has been developed to allow physicians to assess the risk of patients for developing PML. This algorithm is contained in an additional risk minimisation guideline entitled 'Physician Information and Management Guidelines for Multiple Sclerosis patients on TYSABRI Therapy' The risk of PML persists for up to 6 months following discontinuation of Tysabri.
Risk minimisation measures	***Routine risk minimisation measures:*** • Information in SmPC Sections 4.3, 4.4, 4.8, and 5.1; and PL Sections 2 and 4. • Legal status: Restricted medical prescription - Tysabri is prescribed and continuously supervised by specialised physicians experienced in the diagnosis and treatment of neurological conditions with timely access to MRI. ***Additional risk minimisation measures:*** • Educational tools for healthcare professionals (Physician Information and Management Guideline • Educational tools for patients/carers (Patient alert card, Tysabri treatment initiation form, Tysabri treatment continuation form and Tysabri discontinuation form)
Additional pharmacovigilance activities	***Additional pharmacovigilance activities***: • Study IMA-06-02 • Study 101MS411 See Section VI:2.3.2 of this summary for an overview of the post-authorisation development plan.
Serious Herpes Infections	
Evidence for linking the risk to the medicine	In clinical trials, herpes infections (Varicella-Zoster virus, Herpes-simplex virus) occurred slightly more frequently in natalizumab-treated patients than in placebo-treated patients. In post marketing experience, serious, life-threatening, and sometimes fatal cases of encephalitis and meningitis caused by herpes simplex or varicella zoster have been reported in multiple sclerosis patients receiving natalizumab. In post-marketing experience, rare cases of acute retinal necrosis (ARN) have been observed in patients receiving natalizumab, with some of these cases having occurred in patients with central nervous system herpes infections (e.g. herpes meningitis and encephalitis).

Important Identified Risks	
Risk factors and risk groups	No specific risk groups have been identified.
Risk minimisation measures	***Routine risk minimisation measures:*** • Information in SmPC Sections 4.3, 4.4 and 4.8, and PL Sections 2 and 4. • Legal status: Restricted medical prescription - Tysabri is prescribed and continuously supervised by specialised physicians experienced in the diagnosis and treatment of neurological conditions with timely access to MRI. ***Additional risk minimisation measures:*** • None
Additional pharmacovigilance activities	***Additional pharmacovigilance activities***: • Study IMA-06-02 See Section VI:2.3.2 of this summary for an overview of the post-authorisation development plan.

Important Potential Risk(s)	
Malignancies	
Evidence for linking the risk to the medicine	This risk is based on the class of product and based on scientific literature. No differences in incidence rates or the nature of malignancies between natalizumab- and placebo-treated patients were observed over 2 years of treatment. However, observation over longer treatment periods is required before any effect of natalizumab on malignancies can be excluded.
Risk factors and risk groups	None known for natalizumab. Based on the available epidemiological data and the review of malignancy cases, there is no evidence to suggest an increased risk for malignancy associated with long-term natalizumab therapy.
Risk minimisation measures	***Routine risk minimisation measures:*** • Information in SmPC Sections 4.3 and 4.8, and PL Section 2. • Legal status: Restricted medical prescription - Tysabri is prescribed and continuously supervised by specialised physicians experienced in the diagnosis and treatment of neurological conditions with timely access to MRI. ***Additional risk minimisation measures:*** • None
Additional pharmacovigilance activities	***Additional pharmacovigilance activities***: • Study IMA-06-02 See Section VI:2.3.2 of this summary for an overview of the post-authorisation development plan.

Missing Information	
PML risk in patients switching from DMTs with immuno-suppressant effect	
Risk minimisation measures	***Routine risk minimisation measures:*** • Information in SmPC Section 4.4. • Legal status: Restricted medical prescription - Tysabri is prescribed and continuously supervised by specialised physicians experienced in the diagnosis and treatment of neurological conditions with timely access to MRI. ***Additional risk minimisation measures:*** • None
Additional pharmacovigilance activities	***Additional pharmacovigilance activities***: • Study 101MS411 See Section VI:2.3.2 of this summary for an overview of the post-authorisation development plan.
Immunogenicity potential of subcutaneously administered Tysabri (anti-natalizumab antibody formation resulting in a potential adverse clinical consequence of serious hypersensitivity reactions, including anaphylaxis)	
Risk minimisation measures	***Routine risk minimisation measures:*** • Information in SmPC Sections 4.2, 4.3, 4.4, 4.8 and 5.2 • Legal status: Restricted medical prescription - Tysabri is prescribed and continuously supervised by specialised physicians experienced in the diagnosis and treatment of neurological conditions with timely access to MRI. ***Additional risk minimisation measures:*** • None
Additional pharmacovigilance activities	***Additional pharmacovigilance activities***: • Study 101MS412 See Section VI:2.3.2 of this summary for an overview of the post-authorisation development plan

VI: 2.3 Post-authorisation development plan

VI: 2.3.1 Studies that are conditions of the marketing authorisation

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

VI: 2.3.2 Other studies in post-authorisation development plan

Other studies in the post authorisation development plan are as follows:

- **Study IMA-06-02 - Tysabri Observational Programme – An observational study using real world data to assess long-term safety in patients with RRMS.**

  Purpose of the study: To assess the long-term safety, and impact on disease activity and progression, of Tysabri (natalizumab) in patients with RRMS in a clinical practice setting. This study aims to address the safety concerns of PML, Serious herpes infection and Malignancies.

- **Study 101MS411 – An observational cohort study utilising data from the United States natalizumab TOUCH prescribing program and select European Union MS Registries.**

  Purpose of the study: To estimate the risk of PML and other serious opportunistic infections among patients switching to Tysabri from the newer DMTs (including fingolimod, dimethyl fumarate, teriflunomide) and from established DMTs (IFN beta and glatiramer acetate). This study aims to address the safety concern of PML risk in patients switching from DMTs with immunosuppressant effect.

- **Study 101MS412 – An Observational Study Utilising Data from EU National MS Registries to Estimate the Incidence of Anti-Natalizumab Antibody Among Patients Who Receive Subcutaneous Administration of Natalizumab for Treatment of RRMS**

  Purpose of the study: The primary objective is to estimate the incidence of ANAs in patients who start receiving natalizumab SC injections and have never received natalizumab or other monoclonal antibodies. This study aims to evaluate the immunogenicity potential of subcutaneously administered Tysabri (anti-natalizumab antibody formation resulting in a potential adverse clinical consequence of serious hypersensitivity reactions, including anaphylaxis).