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.

Overview of disease epidemiology

MS is a medical condition affecting the central nervous system. In MS, inflammation destroys the protective sheath around the nerves. MS usually starts in people who are aged between 20 and 40 years; MS is rare in children, and in adults aged 60 years and older. Approximately twice as many women than men have MS.

The total number of people living with MS worldwide is estimated to be 2-2.5 million. It is difficult to accurately estimate the number of MS patients in Europe, because there are different ways to study MS and differences in the diagnosis of MS. MS is most common in temperate regions, especially those with large populations of Northern European origin. It is estimated that in Europe 93 out of every 100,000 persons have MS and 90% of patients develop a form of MS called relapsing-remitting MS. In relapsing-remitting MS, people have distinct attacks of symptoms which then fade away either partially or completely.

Summary of treatment benefits

Tysabri has been investigated in two main clinical studies, both lasting two years. One study compared Tysabri on its own with a dummy treatment (placebo) in 942 patients. The second study looked at the effect of adding Tysabri to interferon beta-1a (another medicine used in MS) in 1,171 patients. The main measures of effectiveness were the number of relapses, and the changes in the patients' level of disability measured using a standard scale (the Expanded Disability Status Scale).

Tysabri used on its own was more effective than placebo in reducing the number of relapses. After one year of treatment, there was a decrease of about two-thirds in the number of MS relapses in Tysabri-treated patients, in comparison with the patients receiving placebo. Tysabri was also more effective than placebo in reducing the disabling effects of MS: over two years, the risk of disability getting worse was reduced by 42% in comparison with placebo. In a study with interferon beta-1a, the

risk of disability getting worse and the number of relapses was reduced, but the study was not able to show whether these results were due to Tysabri alone or to the combination.

Unknowns relating to treatment benefits

While MS is rare in children, it does occur. We have limited information in children and adolescents and in patients over 65 years of age but there is no evidence to suggest that it is less effective in these patient groups.

Summary of safety concerns

Summary of important identified risks

Risk	What is known	Preventability
Brain infection caused by a virus (Progressive multifocal leukoencephalopathy=PML)	PML is a serious brain infection which can have symptoms similar to MS and can lead to severe disability or death. The risk of PML is higher if the patient has antibodies against the virus that causes PML. The risk of PML also increases the longer a patient is treated with Tysabri, especially if patients are treated for more than 2 years. It is also higher in patients that have been treated with drugs that suppress the immune system known as immunosuppressants. In addition, patients that have not been treated with immunosuppressants are at higher risk if they have high levels of antibodies against the virus that causes PML. PML has occurred up to 6 months after treatment has been stopped. A condition called JCV GCN (JC virus granule cell neuronopathy) is also caused by JC virus and has occurred in some patients who have been given Tysabri. The symptoms of JCV GCN are similar to PML.	PML is not preventable but detecting it early and stopping Tysabri may improve outcome.
Herpes infection An infection caused by a virus	Herpes infections were seen more frequently in the Tysabri treated patients in	No, but serious herpes infections (including herpes infections of the central

Risk	What is known	Preventability
	clinical studies. Most infections were local without complications. Rare reports of herpes infection in the central nervous system have been reported in commercial use. Rare cases of herpes infections of the eye that may cause blindness have been reported in commercial use.	nervous system) are rare
Allergic reactions	These were seen in 4% of patients in clinical trials. Patients are at increased risk if they have received 1-2 doses of Tysabri followed by a gap in treatment and then restart treatment.	Avoid re-starting treatment if allergic reaction occurs particularly in patients who have had a long gap in treatment
Formation of antibodies to Tysabri	In clinical trials 10% of patients had antibodies to Tysabri at least once. Risk may be increased in patients who have received 1 or 2 doses followed by a gap in treatment and then get re-dosed. Antibody formation may result in a decrease in the effect of Tysabri.	None
Injury to the liver	This was not observed in clinical trials. Occurrences of severe liver damage have been seen in commercial use. There are no known risk factors	None. Patients with a past history of an abnormal liver blood test or who have experienced a worsening of abnormal liver blood tests while on Tysabri should be monitored as appropriate for impaired liver function.

GCN = granule cell neuronopathy; JCV = John Cunningham virus; MS = multiple sclerosis; PML = progressive multifocal leukoencephalopathy.

Summary of important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Cancer	There is a theoretical possibility, due to the effect that Tysabri has on the immune system that patients treated with Tysabri may be at an increased risk of developing new cancers. An increased risk has not been observed to date.

Summary of missing information

Risk	What is known
Effects of natalizumab on pregnancy and outcome of pregnancy	Current data do not suggest that Tysabri when taken early in pregnancy has an adverse effect on pregnancy outcome but further data need to be gathered before definitive reassurance can be given.
Risk of PML in patients switching to Tysabri from other drugs used in treatment of MS which suppress the immune system	Limited data available
Patients over the age of 65 years	Current data do not suggest that the safety of Tysabri in patients over 65 years of age is different to that in younger patients
Paediatric population	Limited number of children or adolescents have been treated. The side effects seen in this population are the same as in adults.
Pharmacokinetic and safety profiles of natalizumab in patients with renal and hepatic impairment	Limited data available

MS = multiple sclerosis; PML = progressive multifocal leukoencephalopathy.

Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

The Summary of Product Characteristics and the Package leaflet for Tysabri can be found in Tysabri's EPAR page.

This medicine has special conditions and restrictions for its safe and effective use (additional risk minimisation measures). Full details on these conditions and the key elements of any educational material can be found in Annex II of the product information which is published in Tysabri's EPAR page; how they are implemented in each country however will depend upon agreement between the manufacturer and the national authorities.

These additional risk minimisation measures are for the following risks:

Safety concern in lay terms (medical term)

Brain infection caused by a virus (Progressive multifocal leukoencephalopathy)

Risk minimisation measure(s) Health care professional and patient education
Objective and rationale
To educate patients and health care professionals so that they understand the risk of PML, the risk factors that lead to the occurrence of PML, how to recognise possible symptoms of PML, and how to treat PML and any events associated with it. This also includes advisement to perform more frequent abbreviated MRI imaging every 3-6 months for patients at higher risk for PML while receiving Tysabri as well as for 6 months following treatment discontinuation. For those patients that are not assessed as at a higher risk for PML, MRI imaging should occur on an annual basis while on therapy and continue for the 6 month period following treatment discontinuation.
Proposed action: HCP educational materials to be provided to prescribing physicians and pharmacists including advice on: Factors which might increase a patient's risk, the diagnosis of PML, treatment of PML as well as routine MRI imaging based on the patient's assessed risk for developing PML. Patient alert card helps patients to identify possible symptoms of PML and the importance of telling their health care professional and to remain aware for symptoms that might arise for up to 6 months after stopping Tysabri treatment. Treatment initiation and continuation forms inform patients and help them make treatment decisions Discontinuation form to remind prescribers and inform patients to continue same MRI monitoring frequency as on treatment for up to 6 months after stopping Tysabri treatment as well as remain vigilant for symptoms of PML that might arise for during this period.

HCP = healthcare professional; MRI = magnetic resonance imaging; PML = progressive multifocal leukoencephalopathy.

Allergic reactions (Hypersensitivity)

Risk minimisation measure(s) Health care professional education
Objective and rationale
To inform physicians about allergic reactions and when they are most likely to occur with Tysabri
Proposed action: HCP educational materials to be provided to prescribing physicians and pharmacists including advice on: • Allergic reactions and when they are most likely to occur with Tysabri. • How to reduce a risk of hypersensitivity • Requirement for monitoring of patients during infusion • Management of allergic reactions including discontinuation of Tysabri

HCP = healthcare professional.

Planned post-authorisation development plan

List of studies in post-authorisation development plan

Study/activity (including study number)	Objectives	Safety concern/ Efficacy issue addressed	Status	Planned date for submission of (interim and final) results
Tysabri Observational Study (TOP) Study IMA-06-02 **Category 3**	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	PML and other infections Malignancies Anti-natalizumab antibody formation Hypersensitivity reactions	Ongoing	Annually
Observational cohort study utilizing the Tysabri TOUCH programme (5 year enrolment: January 2016 – December 2020 + 3 year follow-up) including a feasibility assessment for inclusion of EU registry data. **Category 3**	To estimate the risk of PML among patients on Tysabri switching from the newer DMTs (including fingolimod, dimethyl fumarate, teriflunomide) and from established DMTs (interferon beta and glatiramer acetate)	PML risk in patients switching from DMTs with immuno-suppressant effect	Planned	1) Report on the assessment of the feasibility of including data from the EU utilising existing registries : December 2016 2) Annual interim analysis from August 2017 (updated risk estimates among the DMT groups of interest, stratified by JCV, duration of exposure to Tysabri, prior IS) to be submitted with the annual PSUR 3) Final report: End Q2 2024

DMT = disease modifying therapy; EU = European Union; IS = immunosupressant; JCV = John Cunningham virus; PML = progressive multifocal leukoencephalopathy; PSUR = periodic safety update report; RRMS = relapsing-remitting MS; Q2 = second quarter.

Studies which are a condition of the marketing authorisation

None of the above studies are conditions of the marketing authorisation.

Summary of changes to the risk management plan over time

Version	Date		Safety Concerns	Comment
18			Missing information-PML risk in patients switching from DMTs with immunosuppressant effect	The indication has been modified to allow for patients to switch from newer DMTs with immunosuppressant effect, which were not available at the time of initial marketing authorisation
21	Mar 2016		PIP completed	
22	Jun 2016		Inclusion of ARN under identified risk Herpes infections	
23	Nov 2016		Tygris data included under important identified risk: PML, Herpes infections hypersensitivity, hepatic injury, and under important potential risk Malignancies. Stratify 2 data also included under PML risk.	RMP updated to be in line with the GVP template. Information that was duplicated was removed from the RMP.

ARN = acute retinal necrosis; DMT = disease modifying therapy; GVP = good pharmacovigilance practices; PML = progressive multifocal leukoencephalopathy; RMP = risk management plan.