▼This medicine is subject to additional monitoring. As TYSABRI is a biological medicine, healthcare professionals should report adverse reactions by brand name and batch number.

Physician* Information and Management Guidelines for Patients With Multiple Sclerosis Receiving TYSABRI▼ Therapy

Version 18: [28th January 2020]

***TYSABRI therapy is to be initiated and supervised by specialised physicians experienced in the diagnosis and treatment of neurological conditions in centres with timely access to magnetic resonance imaging (MRI)**

Table of Contents

List of Tables

List of Figures

1 Introduction

This guidance document has been developed for those physicians initiating and supervising TYSABRI in accordance with the conditions of the Marketing Authorisation of the drug, in order to ensure its safe and effective use. It contains information to be used in conjunction with the TYSABRI Summary of Product Characteristics (SmPC) [Appendix 1] and is supported by the Treatment Initiation Form, Treatment Continuation Form, and Treatment Discontinuation Form (Appendix 4). This guidance provides additional risk mitigation measures; for primary guidance, please see the SmPC.

The physician pack also includes a copy of the Package Leaflet (PL) and Patient Alert Card (Appendix 2 and Appendix 3).

It is recommended that physicians initiating and supervising treatment with TYSABRI should share relevant sections of this document with radiologists who are involved in the differential diagnosis of progressive multifocal leukoencephalopathy (PML).

The guidance document focuses primarily on PML, which currently remains the most important adverse reaction affecting patients treated with TYSABRI, and provides practical advice to physicians that is not available through the SmPC.

Other important safety issues associated with TYSABRI, and information about the patient populations suitable for treatment with TYSABRI, are fully described in the SmPC, and physicians should ensure that this guidance document is used together with the SmPC.

2 Opportunistic Infections Including PML

Prescribers should be aware of the possibility that PML and other opportunistic infections may occur during TYSABRI therapy and should include these events in the differential diagnosis of all infections that occur in TYSABRI-treated patients. Cases of PML have also been reported in patients up to 6 months after the last dose of TYSABRI. Patients and their partners and caregivers also need to be advised of symptoms that may be indicative of early PML and continue to be vigilant for approximately 6 months after discontinuation (see Section Patient Alert Card, Appendix 3, and Appendix 4).

If an opportunistic infection is suspected, dosing with TYSABRI must be suspended until it can be excluded through further evaluations.

2.1 *Definition*

An opportunistic infection is defined as an infection due to an organism that generally does not cause disease or that causes only mild or self-limited disease in people with normally functioning immune systems but causes more significant disease in people with impaired immunity.

2.2 *Herpes Infections*

TYSABRI increases the risk of developing encephalitis, meningitis, and acute retinal necrosis (ARN) caused by herpes simplex and varicella zoster viruses:

- Encephalitis, meningitis: In postmarketing experience, serious, life-threatening, and sometimes fatal cases have been reported in patients with multiple sclerosis (MS) receiving TYSABRI.
- ARN: This is a rare fulminant, potentially blinding, viral infection of the retina. In postmarketing experience, rare cases of ARN have been observed in patients receiving TYSABRI; some cases have occurred in patients with central nervous system (CNS) herpes infections (e.g., herpes meningitis and encephalitis). Patients presenting with eye symptoms such as decreased visual acuity, redness, and painful eyes should be referred for retinal screening for ARN.

2.3 *Progressive Multifocal Leukoencephalopathy*

2.3.1 Epidemiology

PML is a subacute, evolving infectious disease of the CNS caused by John Cunningham virus (JCV). It has been described since the 1930s, and the term was first used in 1958. It was first described as a rare complication of lymphoproliferative diseases in middle-aged and elderly patients [Astrom 1958]. Cases have also been reported as a consequence of immunosuppressant (IS) treatment of patients with autoimmune disorders and solid organ transplant recipients.

A seroprevalence study utilising the serum anti-JCV antibody assay (STRATIFY JCV) in over 6000 patients with MS demonstrated the prevalence of anti-JCV antibodies to be approximately 55%. Anti-JCV antibody prevalence in the European Union was reported as ranging from 48.8% to 69.5% in a cross-sectional study of patients with MS, irrespective of treatment [Bozic 2014]. In the MS population, anti-JCV antibody prevalence increased with age and was lower in women than in men in all cohorts

tested. These findings are consistent with those reported in the literature in healthy adults that used similar methodologies [Egli 2009; Kean 2009; Knowles 2003; Stolt 2003]. In general, anti-JCV antibody prevalence did not appear to be affected by prior IS use, prior exposure to TYSABRI, or duration of TYSABRI exposure.

2.3.2 Aetiology

PML affects the subcortical white matter [Safak and Khalili 2003] and is caused by the reactivation of JCV, a human polyomavirus [Berger 1998]. Initial infection with JCV is thought to occur during early childhood, after which the virus persists primarily in the kidneys. Infection with the archetypal virus does not cause disease. However, mutations in the noncoding region and then the capsid protein-coding region of the viral deoxyribonucleic acid (DNA) are thought to lead to a pathogenic form that can enter the brain and infect the CNS. When coupled with a compromised immune system (e.g., from human immunodeficiency virus [HIV] infection, systemic immunosuppression, use of antineoplastic agents, or some malignancies), reactivation of this neurotropic virus can occur, resulting in PML [Berger and Khalili 2011; Gorelik 2011; Kappos 2007; Khalili 2007; Reid 2011; Van Loy 2013; White and Khalili 2011].

2.3.3 Pathology

Replication of JCV in the brain causes a lytic infection of oligodendrocytes resulting in the widespread destruction of myelin. Microscopic lesions develop in the subcortical white matter, which enlarge and may coalesce with a characteristic pattern on magnetic resonance imaging (MRI) examination.

Besides oligodendrocytes, JCV can also infect cerebellar granule cell neurons, resulting in JCV granule cell neuronopathy (GCN). JCV GCN is associated with mutations in the C-terminus of the JCV VP1 gene, coding for the major capsid protein. JCV GCN can occur in isolation or in combination with PML. There have been very rare reports of JCV GCN in patients receiving TYSABRI [Agnihotri 2014; Schippling 2013].

2.3.4 PML in TYSABRI-Treated Patients

During extended preregistration trials, 2 cases of PML were reported in patients with MS and a full safety evaluation revealed 1 additional case in a clinical trial patient with Crohn's disease [Yousry 2006]. In the postmarketing setting, the risk of PML has been well characterised over the first 6 years of treatment with the identification of different levels of PML risk in different patient subgroups (see Section PML Risk Factors).

2.3.5 PML Risk Factors

The following risk factors have been associated with the development of PML during TYSABRI therapy:

- **The presence of anti-JCV antibodies in blood or serum.** Patients who are anti-JCV antibody positive are at an increased risk of developing PML compared with patients who are anti-JCV antibody negative. However, PML only occurs in a minority of patients who are anti-JCV positive because JCV infection is only one of several steps required for the development of PML. The anti-JCV antibody assay is of greatest utility in stratifying PML risk when a positive test result is used in combination with the other identified risk factors described below.
- **Treatment duration**. The risk of PML increases with TYSABRI therapy duration, especially beyond 2 years.

- **Prior immunosuppressant therapy**. Patients who have a history of treatment with an IS prior to starting TYSABRI are also at increased risk of developing PML.

Patients who have all 3 risk factors for PML (i.e., are anti-JCV antibody positive, have received more than 2 years of TYSABRI therapy, and have received prior IS therapy) have a higher risk of PML. In anti-JCV antibody-positive TYSABRI-treated patients who have not used prior IS therapies, 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 with 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 receiving treatment with TYSABRI for longer than 2 years [Ho 2017].

Irrespective of the presence or absence of PML risk factors, heightened clinical vigilance for PML should be maintained in all patients treated with TYSABRI and for 6 months after discontinuation of therapy.

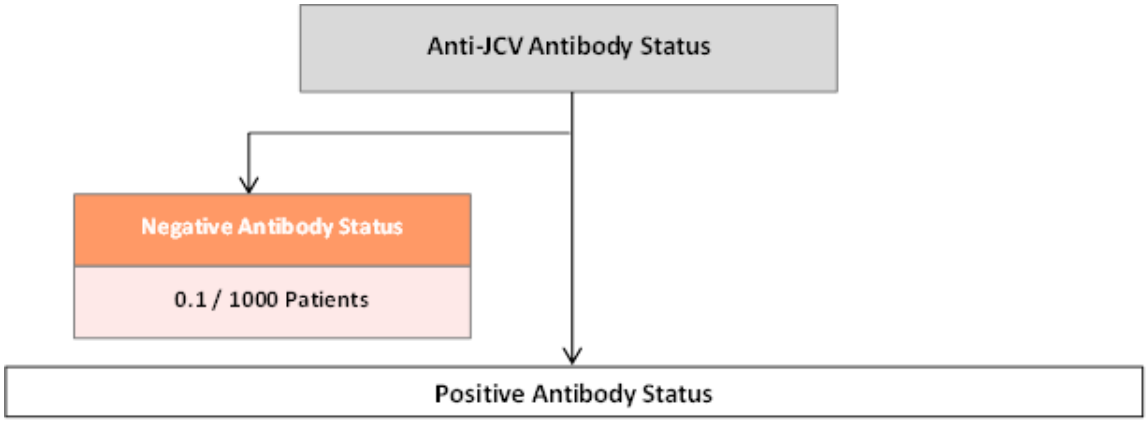
The PML Risk Estimates Algorithm (**Figure 1**) summarises PML risk by anti-JCV antibody status, prior IS use, and duration of TYSABRI therapy (by year of treatment) and stratifies this risk by index value when applicable.

- For anti-JCV antibody-negative patients: PML risk estimates are based on postmarketing data from approximately 125,000 TYSABRI-exposed patients where the estimated incidence of PML for anti-JCV antibody-negative patients is 0.1/1000. 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.

- For anti-JCV antibody-positive patients: Risk estimates were derived using the Life Table Method based on the pooled cohort of 21,696 patients who participated in the STRATIFY-2, TOP, TYGRIS, and STRATA clinical trials. The risk estimates from the Life Table Method are forward-looking in yearly intervals (for example, the risk estimate corresponding to the 25- to 36-month TYSABRI exposure period is the PML risk estimated for the next year for patients treated for 24 months with TYSABRI). The individual treatment length of each patient is taken into consideration with drop-outs (e.g., treatment discontinuation) accounted for.
- For anti-JCV antibody-positive patients who have not used prior IS therapies: The index can further stratify PML risk in patients treated with TYSABRI. A higher anti-JCV antibody index is associated with an increased risk of PML.

- For anti-JCV antibody-positive patients who have used IS previously: These patients are at an increased risk of PML because prior IS use is recognised as an independent risk factor for PML. PML risk estimates for this patient population are based on TYSABRI clinical trial data where prior IS use comprised the following 5 IS therapies: mitoxantrone, methotrexate, azathioprine, cyclophosphamide, and mycophenolate mofetil. The exact mechanism by which these 5 IS therapies lead to an increased PML risk is unknown. In patients with prior IS, current data do not show an association between higher index and PML risk. The underlying biological explanation for this effect is unknown.

Figure 1: PML Risk Estimates Algorithm

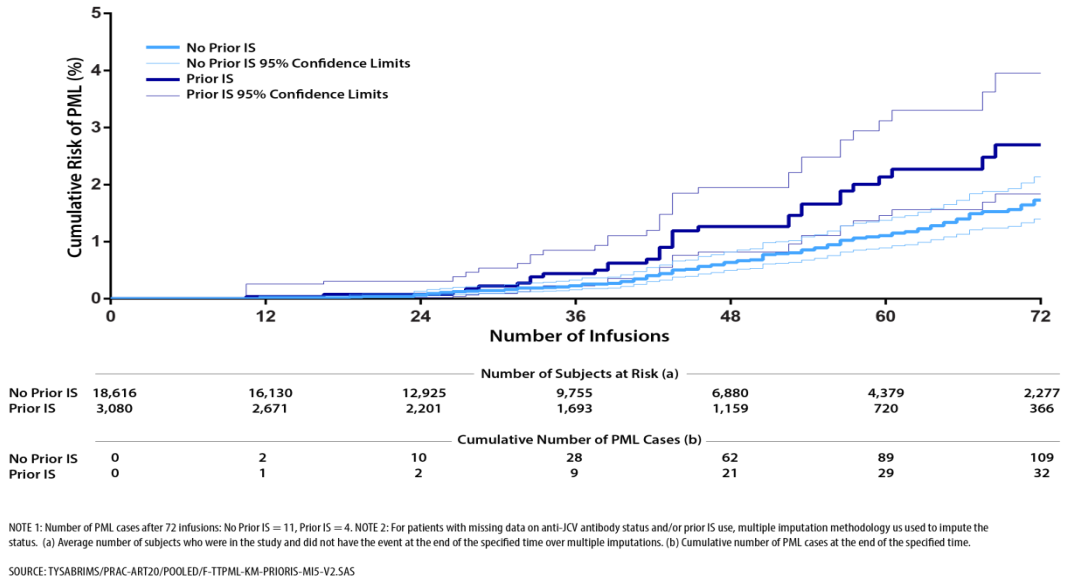


Natalizumab Exposure	PML risk estimates per 1000 patients				
	Patients without prior IS use				Patients with Prior IS use
	No index value	Antibody Index ≤ 0.9	Antibody Index > 0.9 ≤ 1.5	Antibody Index > 1.5	
1-12 months	0.1	0.1	0.1	0.2	0.3
13-24 months	0.6	0.1	0.3	0.9	0.4
25-36 months	2	0.2	0.8	3	4
37-48 months	4	0.4	2	7	8
49-60 months	5	0.5	2	8	8
61-72 months	6	0.6	3	10	6

IS = immunosuppressant; JCV = John Cunningham virus; PML = progressive multifocal leukoencephalopathy.
PML risk estimates in anti-JCV antibody-positive patients were derived using the Life Table Method based on the pooled cohort of 21,696 patients who participated in the STRATIFY-2, TOP, TYGRIS, and STRATA clinical trials. Further stratification of PML risk by anti-JCV antibody index interval for patients with no prior use of IS were derived from combining the overall yearly risk with the antibody index distribution.
PML risk estimates in anti-JCV antibody patients with prior IS exposure are based on TYSABRI clinical data where prior IS use comprised the following IS therapies: mitoxantrone, methotrexate, azathioprine, cyclophosphamide, and mycophenolate mofetil. The risk of PML in anti-JCV antibody-negative patients was estimated based on postmarketing data from approximately 125,000 TYSABRI-exposed patients. Exposure is shown up to 72 months only as data beyond 6 years of treatment are scarce.

Additionally, some physicians may find a Kaplan-Meier (KM) curve useful to provide a visual representation of cumulative PML risk over time using a time-to-event analysis (**Figure 2**). In the KM curve, PML risk estimates for a given timepoint represent the total cumulative risk up to that timepoint (for example, at the timepoint of 48 months, the risk estimate on the KM curve represents the total risk up to 48 months, not the risk between 24 months and 48 months). Like **Figure 1**, data for these analyses were also obtained from the pooled cohort of 21,696 patients who participated in the STRATIFY-2, TOP, TYGRIS, and STRATA clinical trials and also take the individual treatment length of each patient into consideration with drop-outs (e.g., treatment discontinuation) into account.

Figure 2: Cumulative PML Risk Over Time for Anti-JCV Antibody-Positive Patients Stratified by Prior IS



IS = immunosuppressant; JCV = John Cunningham virus; PML = progressive multifocal leukoencephalopathy.
Note: number of PML cases after 72 infusions: No Prior IS = 11, Prior IS = 4.
For patients with missing data on anti-JCV antibody status and/or prior IS use, multiple imputation methodology is used to impute the status. (a) Average number of subjects who were in the study and did not have the event at the end of the specified time over multiple imputations. (b) Cumulative number of PML cases at the end of the specified time.
Source: TYSABRIMS/PRAC-ART20/POOLED/F-TTPML-KM-PRIORIS-MI5-V2-SAS

2.3.6 Extending the Dosing Interval for PML Risk Mitigation

It should be noted that the only approved dosing interval for TYSABRI is 300 mg administered by intravenous infusion once every 4 weeks. Refer to the SmPC Section 4.2 (Posology and method of administration) for the currently approved dosing.

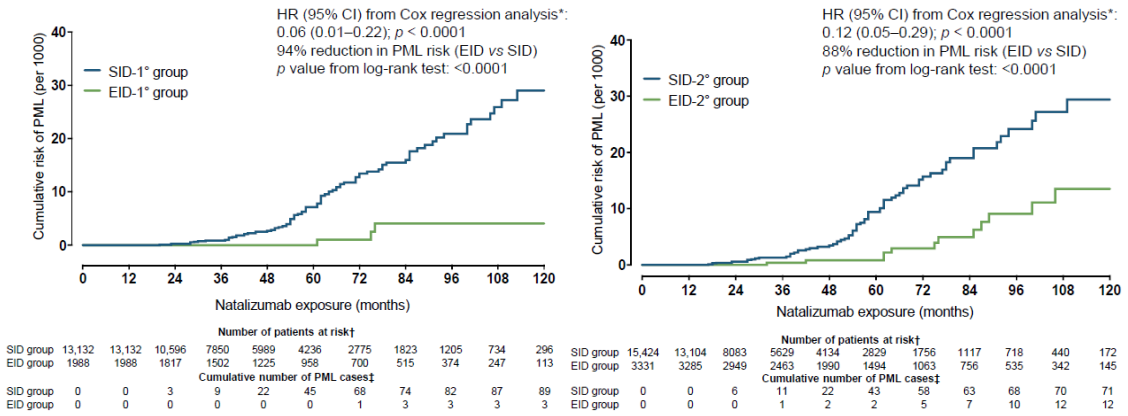
Current real-world data support that there is a significant reduction in the risk of PML in anti-JCV antibody-positive patients treated with an average TYSABRI dosing interval of approximately 6 weeks compared with the approved dosing regimen, which is every 4 weeks (refer to the SmPC Section 5.1 [Pharmacodynamic effects]). In accordance with SmPC Section 4.4 (Special warnings and precautions for use), caution is required if extending the dosing interval of TYSABRI as no prospective randomised controlled clinical trials have been completed to evaluate the efficacy of 6-weekly dosing, and the benefit/risk ratio for any dosing interval other than every 4 weeks has not been established. The efficacy, tolerability, and safety of extending the dosing interval to every 6 weeks in patients who are stable on 4-weekly dosing for ≥ 1 year is currently being studied in a prospective, randomised, controlled clinical trial ('NOVA' study [109MS329], https://www.clinicaltrialsregister.eu/; https://clinicaltrials.gov, NCT03689972).

Summary results from real-world data on extended interval dosing

In 2017, a prespecified, retrospective analysis of anti-JCV antibody-positive patients receiving TYSABRI in the United States was conducted to compare the risk of PML between patients who received the approved dose and those who received extended interval dosing (EID). As there was no consensus on a single definition of EID practice, 3 definitions were prespecified to address different treatment practices; however, PML cases were only observed for the primary and secondary definitions.

The primary definition identified EID based on the last 18 months of TYSABRI exposure. Subsequent analyses showed that the majority of the included EID patients had received the approved dose during the first 18 months of TYSABRI exposure and the median number of infusions EID patients received on or after the start of the defined EID period was between 12.0 and 17.0 infusions across the primary and secondary definitions. The secondary definition identified EID periods of ≥ 6 months occurring at any time during the treatment history with the majority of EID patients included having switched to EID after > 1 year of the approved dose (median 25 doses). For both definitions, EID patients had average dosing intervals of approximately 6 weeks. KM estimates of time to PML and hazards of PML for EID versus the approved dose are presented in **Figure 3**. The analyses concluded that EID treatment, after a period receiving the approved dosing interval, is associated with a statistically and clinically significant lower risk of PML than the approved dose in anti-JCV antibody-positive patients. Efficacy data were not available within this dataset, preventing any conclusions on EID benefit/risk. Although, according to this analysis, the risk of PML in EID patients may be lower, patients treated with EID should receive monitoring for PML following the same guidance as provided for patients receiving the approved dose (SmPC Section 4.4 [Special warnings and precautions for use]).

Figure 3: Kaplan-Meier Estimates of the Cumulative Risk of PML for Primary (A) and Secondary (B) EID Analyses



CI = confidence interval; EID = extended interval dosing; HR = hazard ratio; PML = progressive multifocal leukoencephalopathy; SID = standard interval dosing.
*EID versus SID Cox model includes age, sex, prior use of immunosuppressant therapy, EID/SID group, and calendar year at the start of TYSABRI therapy as covariates.
†Number of patients who were still in the study and did not have PML at the end of the specified time.
‡Cumulative number of PML cases at the end of the specified time.

Results from efficacy modelling data

Previous exposure/response models [Muralidharan 2017] suggested that efficacy would be lower if patients initiated TYSABRI with dosing other than 300 mg every 4 weeks.

Independent publications reporting treatment effectiveness with longer dosing intervals in clinical practice were conducted in patient populations that initially received 4-weekly dosing and subsequently switched to longer dosing intervals [Bomprezzi and Pawate 2014; Yamout 2018; Zhovtis Ryerson 2016]. Updated pharmacokinetic (PK)/pharmacodynamic (PD)/efficacy models from clinical trial data run by the Marketing Authorisation Holder (MAH) suggest that the efficacy of 6-weekly dosing is more comparable to the approved dose if patients are switched to 6-weekly dosing after ≥ 1 year of treatment with the approved dose. PK/PD/efficacy models using data from RESTORE [Fox 2014] (n = 175), which included only patients who had ≥ 1 year of treatment with the approved dose without relapse in the prior year, were developed to explore the risk of MS disease activity return for patients with different body weights (40-59 kg, 60-79 kg, 80-99 kg, 100-120 kg) and dosing intervals (once every 5 weeks, once every 6 weeks, once every 7 weeks, and once every 8 weeks). The models suggest that the risk of return of MS disease activity for patients switching to longer dosing intervals increases with body weight (especially ≥ 80 kg) and length of dosing interval (especially ≥ 7 weeks) [Chang 2019]. No prospective studies have been completed to validate these models. It is recommended that physicians monitor any patients who switch dosing intervals for potential signs of return of MS disease activity in the same way that they would for patients who switch to another therapy, and refer to information provided in the SmPC and this document. More frequent monitoring is recommended for patients with higher body weight (≥ 80 kg) or longer dosing intervals (≥ 7 weeks).

2.3.7 Recommended Patient Monitoring

2.3.7.1 Testing for Anti-JCV Antibodies

Testing serum for anti-JCV antibodies provides supportive information for risk stratification of TYSABRI therapy. Testing for serum anti-JCV antibodies prior to initiating TYSABRI therapy or in patients receiving TYSABRI with an unknown antibody status is recommended. 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. Retesting of anti-JCV antibody-negative patients and low index patients who have no history of prior IS use every 6 months once they reach 2 years of treatment is recommended to inform on appropriate patient MRI monitoring.

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.

Testing should only be performed using an appropriate and validated assay e.g., STRATIFY JCV® DxSelect™ [Lee 2013]. The anti-JCV antibody assay should not be used to diagnose PML. Anti-JCV antibody testing should not be performed during or for at least 2 weeks after plasma exchange (PLEX) due to the removal of antibodies from the serum.

2.3.7.2 Recommended MRI Monitoring for Early Detection of PML

In the clinical practice, MRI has been shown to be a useful tool for monitoring patients with MS. It may assist in differentiating PML lesions from MS plaques in patients who develop new neurological symptoms or signs once on therapy. Frequent MRI surveillance in patients at high risk of PML may lead to an earlier diagnosis of PML

and better clinical outcomes [Prosperini 2016; Scarpazza 2019; Wattjes 2015]. Recommendations for MRI monitoring are summarised below:

a) **Before initiation of treatment with TYSABRI, a recent (usually within 3 months) full MRI (Table 1) should be available as a reference and be repeated at least on a yearly basis.** Physicians should evaluate the yearly full MRI in all patients receiving TYSABRI for any signs of PML.
b) **More frequent MRIs (e.g., on a 3- to 6-monthly basis) using an abbreviated protocol (Table 1) should be considered for patients at a higher risk of PML**. This includes the following:

- Patients who have all 3 risk factors for PML (i.e., are anti-JCV antibody positive **and** have received more than 2 years of TYSABRI therapy **and** have received prior IS therapy)

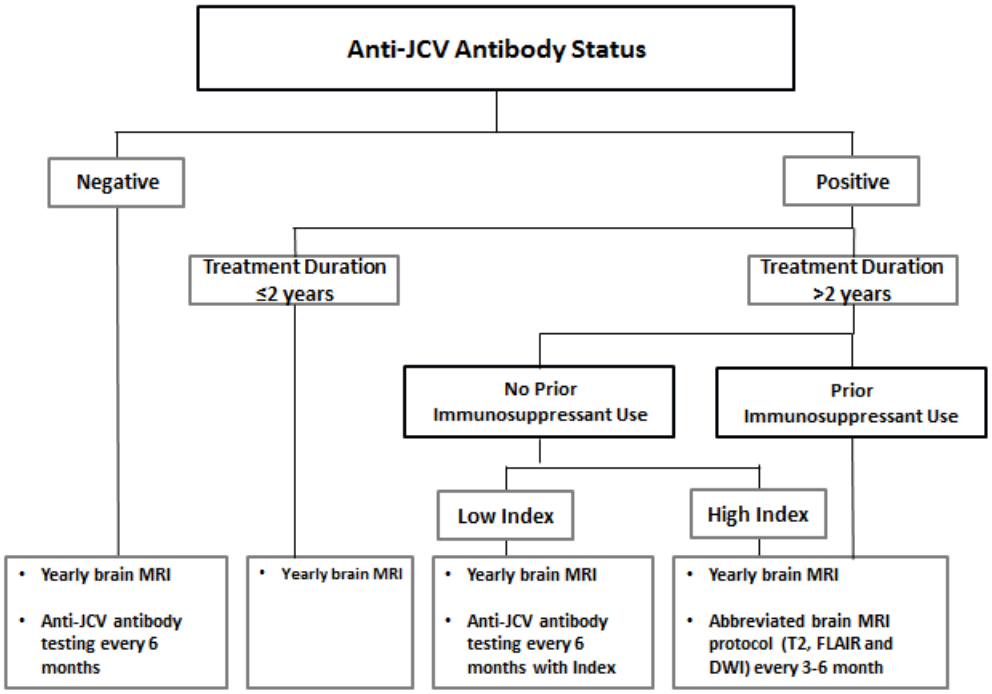
  or

- Patients with a high anti-JCV antibody index who have received more than 2 years of TYSABRI therapy and without prior history of IS therapy.

Current 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 receiving treatment with TYSABRI for more than 2 years. MRI monitoring decisions should take this evidence into consideration, and physician discretion is advised for those patients with index values between 0.9 and 1.5.

***A summary of the recommended monitoring is provided in* Figure 4.**

Figure 4: Recommended Patient Monitoring



DWI = diffusion-weighted imaging; FLAIR = fluid-attenuated inversion recovery; JCV = John Cunningham virus; MRI = magnetic resonance imaging.

Table 1: MRI Protocols
Scanner field strength > 1. 5 T, slice thickness ≤ 5 mm with no gap and with whole brain coverage. Axial images prescribed from the subcallosal line.

Full MRI Protocol (Baseline and routine annual scans for all patients)	**Abbreviated MRI protocol** (Safety monitoring in high-risk patients)
• Sagittal and axial 2D FLAIR or 3D FLAIR • Axial FSE proton density/T2 • Axial DWI with ADC • Axial SE T1-weighted pre- and post-contrast or 3D T1-weighted pre- and post-contrast • Gd injection 0.1 mmol/kg over 30 seconds • 5-minute delay after contrast injection	• Sagittal and axial 2D FLAIR or sagittal 3D FLAIR with axial and coronal reformat • Axial FSE proton density/T2 • Axial DWI with ADC

2D = 2 dimensional; 3D = 3 dimensional; ADC = apparent diffusion coefficient; DWI = diffusion weighted imaging; FLAIR = fluid-attenuated inversion recovery; FSE = fast spin echo; Gd = gadolinium; MRI = magnetic resonance imaging; SE = spin echo.

If MRI lesions suggestive for PML are detected, the full MRI protocol should be extended to include contrast-enhanced T1-weighted imaging to detect inflammatory features and the possible coincidence of PML and PML-immune reconstitution inflammatory syndrome (IRIS), particularly during follow-up. It is also recommended that upon request for follow-up MRI, treating physicians inform radiologists that PML or other opportunistic infections are being considered in the differential diagnosis.

2.3.8 Diagnosis of PML

The American Academy of Neurology-published consensus statement on PML diagnostic criteria requires clinical, radiographic, and virologic findings or typical histopathological findings and the presence of JCV [Berger 2013]. These former criteria obviate the need for a brain biopsy but require compatible clinical and MRI findings plus detection of JCV DNA in the cerebrospinal fluid (CSF) by polymerase chain reaction (PCR) for a definite PML diagnosis; however, based on an alternative classification system, physicians are advised that in TYSABRI-treated patients with MS, diagnosis of PML can be considered confirmed in the absence of clinical symptoms [Dong-Si 2012; Dong-Si 2014] (see Section Laboratory Investigation).

The Malta Medicines Authority should be informed about any cases of PML. Report forms can be downloaded from http://www.medicines authority.gov.mt/adrportal and sent by post or email to:
Post: ADR Reporting
Sir Temi Zammit Buildings,
Malta Life Sciences Park,
San Gwann
SGN 3000,
Malta

Email: postlicensing.medicinesauthority@gov.mt

2.3.8.1 General Principles

All TYSABRI-treated patients should have regular clinical follow-up to allow for early detection of changes in neurological status. **If any new neurological symptoms in patients treated with TYSABRI develop, PML should always be considered as a diagnosis.**

Patients and their partners and caregivers need to be advised of symptoms that may be indicative of early PML (see Section Patient Alert Card, Appendix 3, and Appendix 4) and be counselled on the need to be vigilant for these symptoms while the patient is receiving TYSABRI therapy, and also for approximately 6 months after the last dose of TYSABRI (PML has been reported up to 6 months after the last dose of TYSABRI in patients who did not have findings suggestive of PML at the time of discontinuation).

In all cases where further investigation of change in neurological status or change in brain MRI is indicated, TYSABRI must be suspended and not restarted until non-MS pathology has been confidently excluded. Suspension of TYSABRI therapy for a short duration (days or weeks) is not expected to compromise therapeutic efficacy based on the PD of the drug (see Section Extending the Dosing Interval for PML Risk Mitigation**). TYSABRI dosing should only be restarted when the diagnosis of PML is confidently excluded (if necessary, by repeating clinical, MRI and laboratory investigations if suspicion of PML remains).**

The decision to suspend TYSABRI may be based on the initial clinical presentation, MRI findings, the evolution of symptoms or signs, and/or the response to corticosteroid treatment.

TYSABRI should be permanently discontinued if PML is confirmed.

2.3.8.2 Clinical assessment

Any new or recurrent neurological symptoms should prompt careful evaluation in order to ascertain the underlying pathology, and in a patient with MS disease control, such changes warrant a clinical suspicion of PML (or other opportunistic infection). It is important to note that the presence of new onset neurologic symptoms is not required to diagnose PML (in the setting of other confirmatory evidence) and cases of asymptomatic PML have been reported. In both high- and low-risk asymptomatic patients, any new suspected lesion at a recommended MRI evaluation for monitoring PML risk should be carefully evaluated, particularly when an abbreviated protocol has been performed (see Section MRI Differentiation Between PML and MS Relapse). **Table 2** highlights the clinical features that may help differentiate MS from PML. It should be noted that the table is not all inclusive and that there may be a great deal of overlap between symptoms of the 2 conditions. **Physicians should be aware that the clinical features of PML or other opportunistic infections can be difficult to distinguish from MS, especially early in the evolution.** The history and pattern of previous and current symptoms and signs are important to note and will facilitate the management of TYSABRI-treated patients.

Table 2: Clinical Features of MS and PML

	Features Indicative of:	
	MS	**PML**
Onset	Acute	Subacute

	Features Indicative of:	
	MS	**PML**
Evolution	• Over hours to days • Normally stabilise • Resolve spontaneously even without therapy	• Over weeks • Progressive
Clinical Presentation	• Diplopia • Paraesthesia • Paraparesis • Optic neuritis • Myelopathy	• Aphasia • Behavioural or cognitive changes and neuropsychological alteration • Retrochiasmal visual deficits • Hemiparesis • Seizures • Ataxia (for GCN)

GCN = granule cell neuronopathy; MRI = magnetic resonance imaging; MS = multiple sclerosis; PML = progressive multifocal leukoencephalopathy.
Note: PML may present with other clinical features not specified in this table. PML can be detected by MRI prior to the onset of clinical features.
Reference: [Kappos 2011]

If PML is considered in a differential diagnosis, further investigations including MRI evaluation (**Table 3**) and lumbar puncture and CSF evaluation should be undertaken as soon as possible. TYSABRI dosing should be suspended until PML (or another opportunistic infection) can be ruled out.

The presenting PML symptoms reflect the multifocal pattern of demyelination. Visual, motor, and cognitive deterioration are nearly always present in advanced stages of the infection with widespread lesion size, with cortical blindness, marked weaknesses (such as hemiparesis), and behavioural disturbances being common. Other symptoms include sensory deficits, vertigo, and seizures [Berger 1998]. These symptoms, as well as their evolution, can help differentiate the onset of PML from the typical symptoms of a relapse of MS, but some overlap may exist.

Symptoms of JCV GCN are similar to symptoms of PML (i.e., cerebellar syndrome). In JCV GCN, serial MRI of the brain shows severe progressive cerebellar atrophy over several months and JCV DNA is detected in the CSF. Similar to when new neurological symptoms suggestive of PML develop, TYSABRI therapy should be suspended if JCV GCN and/or PML is suspected and permanently discontinued if JCV GCN and/or PML is confirmed.

2.3.8.3 MRI Differentiation Between PML and MS Relapse

A full MRI protocol (**Table 1**), preferably with and without contrast for the follow-up of patients receiving TYSABRI, is proposed to obtain the best possible images to assist with clinical decision making [Yousry 2006; Yousry 2012]. Fluid-attenuated inversion recovery (FLAIR) is the most sensitive sequence for detection of PML [Wattjes 2015]. Diffusion-weighted imaging sequences may also be helpful in distinguishing new lesions from chronic MS plaques and MRI changes from a previous scan [Mader 2003; Wattjes 2015]. The MRI sequence parameters for each scanner should be selected for good representation of CNS anatomy and visualisation of MS lesions. Consistent use of the standard MRI protocol will help with recognition of early alterations on MRI (**Table 3**).

Further information on the differentiation between PML and MS may be found at *Multiple Sclerosis Society of Malta: http://www.msmalta.org/mt/*

Table 3: Features Visualised on MRI
The table shows features to be considered in the differential diagnosis of MS and PML

Feature	MS	PML
Lesion location	Focal, periventricular, or deep white matter. Lesions occur in all areas of the brain, optic nerves, and spinal cord.	Asymmetric, focal, or multifocal. Subcortical or diffuse white matter, cortical grey matter, and deep grey matter, brainstem, middle cerebellar peduncles. PML is not seen in spinal cord or optic nerves.
Lesion shape and lesion borders	Ovoid or flame shape; sharp borders, often perilesional oedema.	Irregular shape, finger-like projections toward the cortex. Ill-defined border toward the white matter, sharp border toward the grey matter.
Mode of extension	Initial enlargement over days or weeks and decrease in size within months.	Progressive increase in size.
Mass effect	Large acute lesions may have mass effect.	No mass effect.
T2-weighted images	Homogeneous hyperintensity with surrounding oedema.	Diffuse hyperintensity often with punctate microcystic inclusions. Perilesional nodules in the vicinity of the primary lesion (milky way galaxy).
T1-weighted images	Acute lesions: hypointense or isointense. Increasing signal intensity over time.	Isointense to hypointense at onset with decreasing signal intensity over time.
FLAIR images	Hyperintense, sharply delineated.	Hyperintense. Most sensitive sequence for detection of PML.
Contrast enhancement in acute lesions	Homogeneous nodular, ring or open ring enhancement conforms to shape and size of the lesion. Resolution over 1-2 months.	43% of lesions show enhancement at the time of presentation. Patchy or nodular appearance. Enhancement does not conform to size or shape of the lesion. Increased enhancement with IRIS.
DWI	Acute lesions hyperintense. Chronic lesions isointense.	Acute lesions hyperintense. Distinguishes new PML lesions within areas of chronic white matter disease. No restriction on ADC.

Feature	MS	PML
Atrophy	Diffuse atrophy with progressive MS disease.	Post PML-IRIS – encephalomalacia and diffuse brain atrophy in the affected areas.

ADC = apparent diffusion coefficient; DWI = diffusion-weighted imaging; FLAIR = fluid-attenuated inversion recovery; IRIS = immune reconstitution inflammatory syndrome; MRI = magnetic resonance imaging; MS = multiple sclerosis; PML = progressive multifocal leukoencephalopathy.
References: [Kappos 2011; Wattjes and Barkhof 2014; Yousry 2012]

2.3.8.4 Laboratory Investigation

The detection of JCV DNA by PCR in the CSF of a symptomatic or asymptomatic patient with MRI findings consistent with PML confirms the diagnosis of PML. However, a negative JCV PCR result should not exclude a possible diagnosis of PML, particularly because small volume lesions are associated with lower viral copy numbers [Wijburg 2018]. If JCV DNA is not detected in CSF and if clinical or MRI-based suspicion of PML persists despite a local or reference laboratory result being negative (i.e., not detected) for JCV DNA by PCR, a repeat lumbar puncture is recommended. Brain biopsy to detect JCV should be considered if JCV DNA is not detected in CSF on repeat testing, especially if the result is based on an assay with a limit of detection (LoD) that is higher than 11 copies/mL.

Assays should be based on quantitative real-time PCR methodology to maximise sensitivity and specificity for detection, and it is recommended to use an assay with an LoD of at least 11 copies/mL. This level of detection is diagnostically relevant because PML has been confirmed in patients with low copy numbers in the CSF.

CSF samples should be analysed as quickly as possible to facilitate the diagnosis of PML. The MAH is not in a position to certify any laboratory. However, the MAH is aware of a central laboratory (Unilabs, Copenhagen, Denmark) that offers a real-time PCR assay specific for detection of JCV DNA in the CSF.

The real-time assay at Unilabs was developed and qualified at the Translational Sciences department within the MAH and transferred to Unilabs for validation and clinical use. The real-time assay at Unilabs has an LoD of 11 copies/mL.

The reference testing laboratories is carried out by Unilabs Denmark vis the Stratify JCV platform.

Details of the procedure for the collection, handling, and transport of samples to the central facility are available from Medical Affairs in your country.

2.3.9 Management of PML

Immune reconstitution

The data available suggest that early PML recognition is important for an optimal clinical outcome [Clifford 2015; Crowder 2005; Dong-Si 2015; Dong-Si 2014; Geschwind 2001; Prosperini 2016; Shitrit 2005] and that TYSABRI should be immediately discontinued on PML suspicion [Clifford 2015; Grebenciucova and Berger 2018].

Rapid removal of TYSABRI from the body using PLEX and/or immunoadsorption (IA) has also been reported with the intention of accelerated restoration of CNS immunosurveillance [Calabrese 2011; Clifford 2015; Clifford 2010; Dahlhaus 2013; Fernández 2013; Ghezzi 2011; Grebenciucova and Berger 2018; Hellwig and Gold

2011; Kappos 2011]. It has been recommended that the need for PLEX should be carefully considered and, if used, that patients should be closely monitored for the development of IRIS (see Section Treatment of Immune Reconstitution Inflammatory Syndrome), which occurs in almost all patients treated with PLEX for TYSABRI-associated PML and appears to occur more rapidly than in patients who are not treated with PLEX [Carruthers and Berger 2014; Clifford 2010]. Based on a retrospective analysis of natalizumab-treated patients since its approval, no difference was observed on 2-year survival after PML diagnosis between patients who received PLEX and those who did not. Physicians should use medical judgement when considering the use of PLEX to treat PML [data on file].

Antivirals and other adjuvants

To date, no clinical trial has demonstrated a beneficial effect of antiviral agents in the management of PML. Mefloquine, an antimalarial quinolone, has been shown to inhibit JCV replication in cultured cells [Brickelmaier 2009], and there are anecdotal reports of its use in the treatment of PML with favourable outcomes [Calic 2015; Clifford 2010; Fabis-Pedrini 2016; Gheuens 2012; Lauda 2015; Lindå and von Heijne 2013; Schröder 2010; Wenning 2009]. However, retrospective analyses have been unable to demonstrate a benefit [Blankenbach 2019; Stefoski 2019; Tan 2011]. Furthermore, an international randomised clinical trial of mefloquine treatment for PML was terminated early after interim analyses showed no evidence of in vivo antiviral activity against JCV and no effect on clinical disability, MRI parameters, or survival; however, as most of the patients were HIV positive, a meaningful analysis of patients with non-HIV-related PML was not possible [Clifford 2013].

Mirtazapine is a 5HT2A serotonin receptor antagonist that is widely used to treat psychiatric disorders. In vitro studies have shown that JCV uses the 5HT2A serotonin receptor and sialylated oligosaccharides for entering the cell [Elphick 2004; Maginnis 2015; Neu 2010], and 5HT2A serotonin receptor antagonists can inhibit JCV infection in human glial cells [Elphick 2004]. Therefore, mirtazapine has been used for treatment of PML on the basis that it might prevent the spread of the virus. However, there is also in vitro evidence that PML-mutant and wild-type JCV strains utilise alternative nonsialylated pathways to infect cells [Geoghegan 2017]. As with mefloquine, anecdotal reports have suggested a benefit of mirtazapine in TYSABRI-associated PML treatment [Calic 2015; Clifford 2010; Fabis-Pedrini 2016; Gheuens 2012; Lauda 2015; Lindå and von Heijne 2013; Schröder 2010; Wenning 2009]. However, benefit could not been confirmed in retrospective analyses [Blankenbach 2019; Stefoski 2019; Tan 2011], although the authors of 1 analysis [Jamilloux 2016] suggested that mirtazapine may increase survival in TYSABRI-associated PML based on an increased 1-year survival rate in 16 patients treated with mirtazapine compared with a previously reported 1-year survival rate in 336 patients where mirtazapine treatment was not assessed [Dong-Si 2015].

Granulocyte colony-stimulating factor has also been used to treat TYSABRI-associated PML. A single medical centre treated 17 patients with filgrastim as an approach to induce immune activation. Eight patients also received PLEX, and IRIS was reported in the majority of patients in the study. Functional outcomes were mixed [Stefoski 2019].

The use of other antiviral agents has been reported in case reports or small case series of TYASBRI-associated PML, but there has been limited evidence of clinical benefit [Eckert 2018; Pavlovic 2015; Williamson and Berger 2017].

2.3.9.1 Treatment of Immune Reconstitution Inflammatory Syndrome

Clinical neurologic deterioration in patients with PML and/or JCV GCN may be caused by JCV-mediated destruction of CNS tissue, or upon restoration of immune function, by an intracerebral immune inflammatory reaction known as IRIS. IRIS is generally suspected when patients with PML exhibit signs of clinical worsening usually, but not always, accompanied by gadolinium enhancement of PML lesions with or without mass effect on brain MRI. The clinical worsening is a result of a local inflammatory reaction, including oedema, and manifests as a worsening of neurological symptoms including hemiparesis, ataxia, speech abnormalities, visual disturbance, cognitive/behavioural changes, and seizures (dependent on the site of IRIS). Severe sequelae can occur including coma and death. Although JCV load in the CSF might be expected to decline in the setting of IRIS, it is also possible that due to the breakdown of the blood-brain barrier and release of JCV from cells lysed during IRIS, it can be increased.

In patients treated with TYSABRI, IRIS has occurred within days to several weeks after TYSABRI removal by PLEX or IA. Although the inflammatory reaction following immune reconstitution may be a necessary step to remove JCV-infected cells, it may become necessary to treat the active immune reaction to prevent potential damage caused by IRIS [Elston and Thaker 2009; Talan 2009], which can be life threatening and may therefore require management in an intensive care unit. Therefore, following PLEX or IA, periodic clinical monitoring of patients, including MRI monitoring, may be useful for the early detection of IRIS. The diagnosis and management of IRIS is a controversial issue and there is no consensus concerning its treatment. However, it has recently been suggested that corticosteroids may be useful to treat IRIS, particularly in patients with severe to life-threatening IRIS [Calabrese 2011; Clifford 2015; Clifford 2010; Scarpazza 2017a; Tan 2011; Tan 2009]. The following steroid regimens have been reported for the treatment of IRIS in the literature:

1. Oral prednisone 1.5 mg/kg/d x 2 weeks with a taper over 2 months
2. Intravenous methylprednisolone (1 g/d for 3 or 5 days) with oral taper over 2 months [Gheuens 2012; Hodecker 2017; Mitsikostas 2014; Purohit 2016].

If further deterioration occurs during the steroid taper and this is judged to be due to continuing or new inflammatory reactions, a further course of higher dose steroids may be necessary.

Prophylactic steroid treatment is currently not recommended [Antoniol 2012; Scarpazza 2017a; Stefoski 2019; Tan 2011]. As scientific and medical knowledge, including both diagnostic criteria and management of IRIS is rapidly evolving, please contact Medical Affairs in your country for the most up-to-date information on treatment recommendations.

Other treatments

There have been some reports on the use of maraviroc, which blocks C-C chemokine receptor type 5-mediated tissue inflammation, to prevent and treat IRIS in patients with TYSABRI-associated PML [Bsteh 2017; Giacomini 2014; Hodecker 2017]. However, its effect on clinical outcome has been disputed [Scarpazza 2017b; Stefoski 2019]. Furthermore, a randomised, placebo-controlled trial of maraviroc in HIV-positive patients failed to show protection from IRIS after antiretroviral therapy initiation [Sierra-Madero 2014].

Intravenous immunoglobulins have also been used to try to slow and treat IRIS in patients with TYSABRI-associated PML. However, data are limited to only a few case

reports, and clinical outcomes have been inconsistent [Calic 2015; Clifford 2010; Kuhle 2011; Lauda 2015; Thaker 2014].

Seizures have been associated with IRIS, and it has been recommended that this risk should also be considered when treating patients for IRIS [Dahlhaus 2013; Hoepner 2014; Mitsikostas 2014]. Mirtazapine and mefloquine can lower the seizure threshold [Dahlhaus 2013; Hoepner 2014], and preventative antiepileptic treatment has been shown to be beneficial in some cases [Hoepner 2014].

As scientific and medical knowledge, including both diagnostic criteria and management of PML and IRIS, is continually evolving, please contact Medical Affairs in your country for the most up-to-date information on treatment recommendations.

2.3.10 Prognosis

Improved survival from PML after TYSABRI therapy has been associated with a younger age at PML diagnosis, less functional disability before PML diagnosis, a lower JCV load at PML diagnosis, and more localised brain involvement on MRI at diagnosis [Dong-Si 2015]. Furthermore, asymptomatic patients at PML diagnosis have been reported to have better survival and less functional disability than symptomatic patients at PML diagnosis [Dong-Si 2014; Prosperini 2016]. For information on outcomes associated with PLEX, see Section Management of PML.

Asymptomatic PML (with a comparison to symptomatic PML)

Cases of asymptomatic PML have been reported that were initially suspected based on MRI findings and later confirmed by positive JCV DNA in the CSF.

Asymptomatic PML patients had a shorter time from suspicion of PML to diagnosis of PML compared with symptomatic PML patients (median of 11 days versus 30 days, respectively). In addition, asymptomatic PML patients had more localised PML on brain MRI at the time of suspicion compared with symptomatic PML patients. There was a higher proportion of asymptomatic PML patients who had unilobar PML lesions on MRI at the time of diagnosis compared with symptomatic PML patients (56.2% versus 36.9%, respectively). Conversely, 18.8% of asymptomatic patients had widespread PML on MRI compared with 40.8% of symptomatic patients.

Asymptomatic PML patients also had a higher survival rate compared with symptomatic patients (92.2% versus 73.1%, respectively).

2.3.11 PML Diagnosed After Discontinuation of TYSABRI

While the majority of cases of PML have occurred during treatment with TYSABRI, there have been reports of cases identified more than 4 weeks after the last infusion. Of the 566 confirmed cases of PML reported as of 04 June 2015, PML onset was known for 98% (555 cases). Seventy-four cases (13%) had PML onset more than 4 weeks after the last infusion of TYSABRI. Eight of these patients (11%) were asymptomatic and initial suspicion of PML was based on MRI findings. Nine patients (12%) died and 65 patients (88%) were alive at the time of the analysis. TYSABRI exposure ranged from 8 to 90 months (mean 43 months; median 42.5 months), with the majority of the patients (81%; 60 of 74) having received > 24 months of treatment. The time between the last TYSABRI infusion and the onset of PML ranged from 1 to 6 months, with a mean of 2.1 months and median of 1.8 months; the majority of cases (88%; 65 of 74) occurred within 3 months of the last infusion of TYSABRI.

Because PML has been reported after the discontinuation of TYSABRI in patients who did not have findings suggestive of PML at the time of discontinuation, patients and physicians should be alert for any new signs or symptoms that may be suggestive of PML. Patients should continue with the same MRI monitoring protocol associated with their level of risk for PML for approximately 6 months after discontinuation, taking into account the switch to other MS disease-modifying treatments that are associated with a potential or identified risk of PML.

3 Educational Guidance

Physicians need to inform patients about the benefits and risks of TYSABRI and provide them with a Patient Alert Card (see Appendix 3) prior to initiation of therapy and to continue to counsel patients on the risk of PML on a regular basis thereafter. Due to this increased risk of developing PML with increasing treatment duration, the benefits and risks of TYSABRI therapy should be individually reconsidered by the specialist physician and the patient. The patient should be reinformed about the risks of PML with TYSABRI after 24 months and should be instructed together with their partners and caregivers on early signs and symptoms of PML. Patients who are discontinuing TYSABRI therapy should also be informed that cases of PML have occurred in patients up to 6 months after the last dose of TYSABRI. In this situation, the same monitoring protocol should be continued for approximately 6 months after discontinuation of TYSABRI. A template Treatment Initiation Form, Treatment Continuation Form, and Treatment Discontinuation Form are provided in Appendix 4.

The Malta Medicines Authority should be informed about any cases of PML. Report forms can be downloaded from http://www.medicines authority.gov.mt/adrportal and sent by post or email to:
Post: ADR Reporting
Sir Temi Zammit Buildings,
Malta Life Sciences Park,
San Gwann
SGN 3000,
Malta

Email: postlicensing.medicinesauthority@gov.mt

3.1 *Informing Patients About Benefits and Risks*

The PL that is contained in each pack of TYSABRI explains both benefits and risks in language designed specifically for patients to understand (this has been confirmed by MS patient readability testing). An example is included as part of this pack (Appendix 2) so that the physician can become familiar with the PL prior to counselling patients about TYSABRI therapy.

Physicians should counsel patients on the importance of uninterrupted dosing, particularly in the early months of treatment.

Physicians should counsel pregnant women on the use of TYSABRI during pregnancy taking into account the patient's clinical condition. This benefit-risk discussion should also cover the possible return of disease activity after stopping TYSABRI and the monitoring of newborns for potential haematological abnormalities for patients exposed to TYSABRI in the third trimester.

In addition, locally agreed templates for a Treatment Initiation Form, a Treatment Continuation Form at 24months of treatment, and a Treatment Discontinuation Form describing specifically the risk of PML with TYSABRI therapy and the importance of monitoring for PML are provided in Appendix 4. These should be provided to and discussed with patients before initiation of treatment, after 24 months of treatment, and after discontinuation to ensure that patients are fully informed about the risk of PML.

The physician should keep 1copy of these forms and 1 copy should be given to the patient

3.2 *Patient Alert Card*

The Patient Alert Card must be issued to patients to fill out and carry with them.

It reminds patients that because of the risks of PML associated with TYSABRI, they must contact their physician if they believe that either their MS is getting worse or they or their family members notice new symptoms such as changes in mood, behaviour, memory, motor weakness, speech, or communication difficulties. Partners and caregivers should also be made aware of the information provided in the Patient Alert Card. The Patient Alert Card includes a recommendation for patients to retain the card for a period of 6 months after the last dose of TYSABRI therapy because signs and symptoms suggestive of PML may occur up to 6 months after discontinuation and patients and their partners and caregivers should report any suspect changes in neurological status during this time.

The card contains a space to provide contact information so that they can report these concerns. Their physician must complete this section when issuing the card.

Patient Alert Cards (see Appendix 3) are included as part of the Physician Pack. Additional cards can be ordered from the local company office; contact details are contained in the pack.

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5 Appendices

5.1 *Appendix 1. Summary of Product Characteristics (SmPC)*

5.2 *Appendix 2. Package Leaflet (PL)*

5.3 *Appendix 3. Patient Alert Card*

5.4 *Appendix 4. Treatment Initiation Form, Treatment Continuation Form, and Treatment Discontinuation Form*

APPENDIX 1

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions

1. NAME OF THE MEDICINAL PRODUCT

TYSABRI 300 mg concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of concentrate contains 20 mg of natalizumab.

When diluted (see section 6.6), the solution for infusion contains approximately 2.6 mg/ml of natalizumab.

Natalizumab is a recombinant humanised anti-α4-integrin antibody produced in a murine cell line by recombinant DNA technology.

Excipient with known effect

Each vial contains 2.3 mmol (or 52 mg) sodium. When diluted in 100 ml sodium chloride 9 mg/ml (0.9%) the medicinal product contains 17.7 mmol (or 406 mg) sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

Colourless, clear to slightly opalescent solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

TYSABRI is indicated as single disease modifying therapy in adults with highly active relapsing remitting multiple sclerosis for the following patient groups:

- Patients with highly active disease despite a full and adequate course of treatment with at least one disease modifying therapy (DMT) (for exceptions and information about washout periods see sections 4.4 and 5.1)

or

- Patients with rapidly evolving severe relapsing remitting multiple sclerosis defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI.

4.2 Posology and method of administration

TYSABRI therapy is to be initiated and continuously supervised by specialised physicians experienced in the diagnosis and treatment of neurological conditions, in centres with timely access to MRI.

Patients treated with TYSABRI must be given the patient alert card and be informed about the risks of the medicinal product (see also package leaflet). After 2 years of treatment, patients should be re-informed about the risks of TYSABRI, especially the increased risk of Progressive Multifocal Leukoencephalopathy (PML), and should be instructed together with their caregivers on early signs and symptoms of PML.

Resources for the management of hypersensitivity reactions and access to MRI should be available.

Some patients may have been exposed to immunosuppressive medicinal products (e.g. mitoxantrone, cyclophosphamide, azathioprine). These medicinal products have the potential to cause prolonged immunosuppression, even after dosing is discontinued. Therefore the physician must confirm that such patients are not immunocompromised before starting treatment with TYSABRI (see also section 4.4).

Posology

TYSABRI 300 mg is administered by intravenous infusion once every 4 weeks.

Continued therapy must be carefully reconsidered in patients who show no evidence of therapeutic benefit beyond 6 months

Data on the safety and efficacy of natalizumab at 2 years were generated from controlled, double–blind studies. After 2 years continued therapy should be considered only following a reassessment of the potential for benefit and risk. Patients should be re-informed about the risk factors for PML, like duration of treatment, immunosuppressant use prior to receiving TYSABRI and the presence of anti-John Cunningham virus (JCV) antibodies (see section 4.4.).

Readministration

The efficacy of re-administration has not been established, for safety see section 4.4.

Special populations

Elderly

TYSABRI is not recommended for use in patients aged over 65 due to a lack of data in this population.

Renal and hepatic impairment

Studies have not been conducted to examine the effects of renal or hepatic impairment.

The mechanism for elimination and results from population pharmacokinetics suggest that dose adjustment would not be necessary in patients with renal or hepatic impairment.

Paediatric population

The safety and efficacy of TYSABRI in children and adolescents up to 18 years have not been established. No recommendation on a posology can be made. Currently available data are described in sections 4.8 and 5.1

Method of administration

TYSABRI is for intravenous use.

For instructions on dilution of the medicinal product before administration, see section 6.6.

After dilution (see section 6.6), the infusion is to be administered over approximately 1 hour and patients are to be observed during the infusion and for 1 hour after the completion of the infusion for signs and symptoms of hypersensitivity reactions.

TYSABRI must not be administered as a bolus injection.

4.3 Contraindications

Hypersensitivity to natalizumab or to any of the excipients listed in section 6.1.

Progressive multifocal leukoencephalopathy (PML).

Patients with increased risk for opportunistic infections, including immunocompromised patients (including those currently receiving immunosuppressive therapies or those immunocompromised by prior therapies (see sections 4.4 and 4.8).

Combination with other DMTs.

Known active malignancies, except for patients with cutaneous basal cell carcinoma.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and batch number of the administered product should be clearly recorded.

Progressive Multifocal Leukoencephalopathy (PML)

Use of TYSABRI has been associated with an increased risk of PML, an opportunistic infection caused by JC virus, which may be fatal or result in severe disability. Due to this increased risk of developing PML, the benefits and risks of TYSABRI treatment should be individually reconsidered by the specialist physician and the patient; patients must be monitored at regular intervals throughout and should be instructed together with their caregivers on early signs and symptoms of PML. JC virus also causes JCV granule cell neuronopathy (GCN) which has been reported in patients treated with TYSABRI. Symptoms of JCV GCN are similar to symptoms of PML (i.e. cerebellar syndrome).

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 TYSABRI.
- Immunosuppressant use prior to receiving TYSABRI.

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 TYSABRI 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.

In anti-JCV antibody positive patients, extended interval dosing of TYSABRI (average dosing interval of approximately 6 weeks) is suggested to be associated with a lower PML risk compared to approved dosing. If utilising extended interval dosing, caution is required because the efficacy of extended interval dosing has not been established and the associated benefit risk balance is currently unknown (see section 5.1). For further information, refer to the Physician Information and Management Guidelines.

In patients considered at high risk treatment with TYSABRI should only be continued if the benefits outweigh the risks. For the estimation of PML risk in the different patient subgroups, please refer to the Physician Information and Management Guidelines.

Anti-JCV antibody testing

Anti-JCV antibody testing provides supportive information for risk stratification of TYSABRI treatment. Testing for serum anti-JCV antibody prior to initiating TYSABRI therapy or in patients receiving the medicinal product with an unknown antibody status is recommended. 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. Re-testing of anti-JCV antibody negative patients every 6 months is recommended. Retesting low index patients who have no history of prior immunosuppressant use every 6 months once they reach the 2 year treatment point is recommended.

The anti-JCV antibody assay (ELISA) should not be used to diagnose PML. Use of plasmapheresis (PLEX) or intravenous immunoglobulin (IVIg) can affect meaningful interpretation of serum anti-JCV antibody testing. Patients should not be tested for anti-JCV antibodies within 2 weeks of PLEX due to removal of antibodies from the serum, or within 6 months of IVIg (i.e. 6 months = 5x half-life for immunoglobulins).

For further information on anti-JCV antibody testing please see Physician Information and Management Guidelines.

MRI screening for PML

Before initiation of treatment with TYSABRI, a recent (usually within 3 months) MRI should be available as a reference, and be repeated at least on a yearly basis. More frequent MRIs (e.g. on a 3 to 6 monthly basis) using an abbreviated protocol should be considered for patients at higher risk of PML. This includes:

- Patients who have all three risk factors for PML (i.e., are-anti-JCV antibody positive **and** have received more than 2 years of TYSABRI therapy, **and** have received prior immunosuppressant therapy),

or

- Patients with a high anti-JCV antibody index who have received more than 2 years of TYSABRI therapy and without prior history of immunosuppressant therapy.

Current 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 2 years (see the Physician Information and Management Guidelines for further information).

No studies have been performed to evaluate the efficacy and safety of TYSABRI when switching patients from DMTs with an immunosuppressant effect. It is unknown if patients switching from these therapies to TYSABRI have an increased risk of PML, therefore these patients should be monitored more frequently (i.e. similarly to patients switching from immunosuppressants to TYSABRI).

PML should be considered as a differential diagnosis in any MS patient taking TYSABRI presenting with neurological symptoms and/or new brain lesions in MRI. Cases of asymptomatic PML based on MRI and positive JCV DNA in the cerebrospinal fluid have been reported.

Physicians should refer to the Physician Information and Management Guidelines for further information on managing the risk of PML in TYSABRI-treated patients.

If PML or JCV GCN is suspected, further dosing must be suspended until PML has been excluded.

The clinician should evaluate the patient to determine if the symptoms are indicative of neurological dysfunction and, if so, whether these symptoms are typical of MS or possibly suggestive of PML or JCV GCN. If any doubt exists, further evaluation, including MRI scan preferably with contrast (compared with pre-treatment baseline MRI), CSF testing for JC Viral DNA and repeat neurological assessments, should be considered as described in the Physician Information and Management Guidelines (see educational guidance). Once the clinician has excluded PML and/or JCV GCN (if necessary, by repeating clinical, imaging and/or laboratory investigations if clinical suspicion remains), dosing of TYSABRI may resume.

The physician should be particularly alert to symptoms suggestive of PML or JCV GCN that the patient may not notice (e.g. cognitive, psychiatric symptoms or cerebellar syndrome). Patients should also be advised to inform their partner or caregivers about their treatment, since they may notice symptoms that the patient is not aware of.

PML has been reported following discontinuation of TYSABRI in patients who did not have findings suggestive of PML at the time of discontinuation. Patients and physicians should continue to follow the same monitoring protocol and be alert for any new signs or symptoms that may be suggestive of PML for approximately 6 months following discontinuation of TYSABRI.

If a patient develops PML the dosing of TYSABRI must be permanently discontinued.

Following reconstitution of the immune system in immunocompromised patients with PML improved outcome has been seen.

PML and IRIS (Immune Reconstitution Inflammatory Syndrome)

IRIS occurs in almost all TYSABRI PML patients after withdrawal or removal of the medicinal product, e.g. by plasma exchange (see section 5.2). IRIS is thought to result from the restoration of immune function in patients with PML, which can lead to serious neurological complications and may be fatal. Monitoring for development of IRIS, which has occurred within days to several weeks after plasma exchange in TYSABRI treated patients with PML, and appropriate treatment of the associated inflammation during recovery from PML should be undertaken (see the Physician Information and Management Guidelines for further information).

Infections including other opportunistic infections

Other opportunistic infections have been reported with use of TYSABRI, primarily in patients with Crohn’s disease who were immunocompromised or where significant co-morbidity existed, however increased risk of other opportunistic infections with use of the medicinal product in patients without these co-morbidities cannot currently be excluded. Opportunistic infections were also detected in MS patients treated with TYSABRI as a monotherapy (see section 4.8).

TYSABRI increases the risk of developing encephalitis and meningitis caused by herpes simplex and varicella zoster viruses. Serious, life-threatening, and sometimes fatal cases have been reported in the postmarketing setting in multiple sclerosis patients

receiving TYSABRI (see section 4.8). If herpes encephalitis or meningitis occurs, the medicinal product should be discontinued, and appropriate treatment for herpes encephalitis or meningitis should be administered.

Acute retinal necrosis (ARN) is a rare fulminant viral infection of the retina caused by the family of herpes viruses (e.g. varicella zoster). ARN has been observed in patients being administered TYSABRI and can be potentially blinding. Patients presenting with eye symptoms such as decreased visual acuity, redness and painful eye should be referred for retinal screening for ARN. Following clinical diagnosis of ARN, discontinuation of TYSBABRI should be considered in these patients.

Prescribers should be aware of the possibility that other opportunistic infections may occur during TYSABRI therapy and should include them in the differential diagnosis of infections that occur in TYSABRI-treated patients. If an opportunistic infection is suspected, dosing with TYSABRI is to be suspended until such infections can be excluded through further evaluations.

If a patient receiving TYSABRI develops an opportunistic infection, dosing of the medicinal product must be permanently discontinued.

Educational guidance

All physicians who intend to prescribe TYSABRI must ensure they are familiar with the Physician Information and Management Guidelines.

Physicians must discuss the benefits and risks of TYSABRI therapy with the patient and provide them with a Patient Alert Card. Patients should be instructed that if they develop any infection then they should inform their physician that they are being treated with TYSABRI.

Physicians should counsel patients on the importance of uninterrupted dosing, particularly in the early months of treatment (see hypersensitivity).

Hypersensitivity

Hypersensitivity reactions have been associated with TYSABRI, including serious systemic reactions (see section 4.8). These reactions usually occurred during the infusion or up to 1 hour after completion of the infusion. The risk for hypersensitivity was greatest with early infusions and in patients re-exposed to TYSABRI following an initial short exposure (one or two infusions) and extended period (three months or more) without treatment. However, the risk of hypersensitivity reactions should be considered for every infusion administered.

Patients are to be observed during the infusion and for 1 hour after the completion of the infusion (see section 4.8). Resources for the management of hypersensitivity reactions should be available.

Discontinue administration of TYSABRI and initiate appropriate therapy at the first symptoms or signs of hypersensitivity.

Patients who have experienced a hypersensitivity reaction must be permanently discontinued from treatment with TYSABRI.

Concurrent treatment with immunosuppressants

The safety and efficacy of TYSABRI in combination with other immunosuppressive and antineoplastic therapies have not been fully established. Concurrent use of these agents with TYSABRI may increase the risk of infections, including opportunistic infections, and is contraindicated (see section 4.3).

In Phase 3 MS clinical trials, concomitant treatment of relapses with a short course of corticosteroids was not associated with an increased rate of infection. Short courses of corticosteroids can be used in combination with TYSABRI.

Prior treatment with immunosuppressive or immunomodulatory therapies

Patients with a treatment history of immunosuppressant medications are at increased risk for PML.
No studies have been performed to evaluate the efficacy and safety of TYSABRI when switching patients from DMTs with an immunosuppressant effect. It is unknown if patients switching from these therapies to TYSABRI have an increased risk of PML, therefore these patients should be monitored more frequently (i.e. similarly to patients switching from immunosuppressants to TYSABRI, see MRI screening for PML).

Care should be taken with patients who have previously received immunosuppressants to allow sufficient time for immune function recovery to occur. Physicians must evaluate each individual case to determine whether there is evidence of an immunocompromised state prior to commencing treatment with TYSABRI (see section 4.3).
When switching patients from another DMT to TYSABRI, the half-life and mode of action of the other therapy must be considered in order to avoid an additive immune effect whilst at the same time minimising the risk of disease reactivation. A Complete Blood Count (CBC, including lymphocytes) is recommended prior to initiating TYSABRI to ensure that immune effects of the previous therapy (i.e. cytopenia) have resolved.

Patients can switch directly from beta interferon or glatiramer acetate to TYSABRI providing there are no signs of relevant treatment-related abnormalities e.g. neutropenia and, lymphopenia.

When switching from dimethyl fumarate, the washout period should be sufficient for lymphocyte count to recover before treatment with TYSABRI is started.

Following discontinuation of fingolimod, lymphocyte count progressively returns to normal range within 1 to 2 months after stopping therapy. The washout period should be sufficient for lymphocyte count to recover before treatment with TYSABRI is started.

Teriflunomide is eliminated slowly from the plasma. Without an accelerated elimination procedure, clearance of teriflunomide from plasma can take from several months up to 2 years. An accelerated elimination procedure as defined in the teriflunomide Summary of Product Characteristics is recommended or alternatively washout period should not be shorter than 3.5 months. Caution regarding potential concomitant immune effects is required when switching patients from teriflunomide to TYSABRI.

Alemtuzumab has profound prolonged immunosuppressive effects. As the actual duration of these effects is unknown, initiating treatment with TYSABRI after alemtuzumab is not recommended unless the benefits clearly outweigh the risks for the individual patient.

Immunogenicity

Disease exacerbations or infusion related events may indicate the development of antibodies against natalizumab. In these cases the presence of antibodies should be evaluated and if these remain positive in a confirmatory test after at least 6 weeks, treatment should be discontinued, as persistent antibodies are associated with a substantial decrease in efficacy of TYSABRI and an increased incidence of hypersensitivity reactions (see section 4.8).

Since patients who have received an initial short exposure to TYSABRI and then had an extended period without treatment are at a higher risk of developing anti-natalizumab antibodies and/or hypersensitivity upon redosing, the presence of antibodies should be evaluated and if these remain positive in a confirmatory test after at least 6 weeks, the patient should not receive further treatment with TYSABRI.

Hepatic events

Spontaneous serious adverse reactions of liver injury have been reported during the post marketing phase. These liver injuries may occur at any time during treatment, even after the first dose. In some instances, the reaction reoccurred when TYSABRI was reintroduced. Some patients with a past medical history of an abnormal liver test have experienced an exacerbation of abnormal liver test while on TYSABRI. Patients should be monitored as appropriate for impaired liver function, and be instructed to contact their physician in case signs and symptoms suggestive of liver injury occur, such as jaundice and vomiting. In cases of significant liver injury TYSABRI should be discontinued.

Stopping TYSABRI therapy

If a decision is made to stop treatment with natalizumab, the physician needs to be aware that natalizumab remains in the blood, and has pharmacodynamic effects (e.g increased lymphocyte counts) for approximately 12 weeks following the last dose. Starting other therapies during this interval will result in a concomitant exposure to natalizumab. For medicinal products such as interferon and glatiramer acetate, concomitant exposure of this duration was not associated with safety risks in clinical trials. No data are available in MS patients regarding concomitant exposure with immunosuppressant medication. Use of these medicinal products soon after the

discontinuation of natalizumab may lead to an additive immunosuppressive effect. This should be carefully considered on a case-by-case basis, and a wash-out period of natalizumab might be appropriate. Short courses of steroids used to treat relapses were not associated with increased infections in clinical trials.

Sodium content in TYSABRI

TYSABRI contains 2.3 mmol (or 52 mg) sodium per vial of medicinal product. When diluted in 100 ml sodium chloride 9 mg/ml (0.9%) this medicinal product contains 17.7 mmol (or 406 mg) sodium per dose. To be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

TYSABRI is contraindicated in combination with other DMTs (see section 4.3).

Immunisations

In a randomised, open label study of 60 patients with relapsing MS there was no significant difference in the humoral immune response to a recall antigen (tetanus toxoid) and only slightly slower and reduced humoral immune response to a neoantigen (keyhole limpet haemocyanin) was observed in patients who were treated with TYSABRI for 6 months compared to an untreated control group. Live vaccines have not been studied.

4.6 Fertility, pregnancy and lactation

Pregnancy

Studies in animals have shown reproductive toxicity (see section 5.3).

Data from clinical trials, a prospective pregnancy registry, post-marketing cases and available literature do not suggest an effect of TYSABRI exposure on pregnancy outcomes.

The completed prospective TYSABRI pregnancy registry contained 355 pregnancies with available outcomes. There were 316 live births, 29 of which were reported to have birth defects. Sixteen of the 29 were classified as major defects. The rate of defects corresponds to the defect rates reported in other pregnancy registries involving MS patients. There is no evidence of a specific pattern of birth defects with TYSABRI.

Cases from published literature reported transient mild to moderate thrombocytopenia and anaemia observed in infants born to women exposed to TYSABRI in their third trimester of pregnancy. Therefore, it is recommended that newborns of women exposed to the medicinal product during the third trimester of pregnancy are monitored for potential haematological abnormalities.

If a woman becomes pregnant while taking TYSABRI, discontinuation of the medicinal product should be considered. A benefit-risk evaluation of the use of TYSABRI during

pregnancy should take into account the patient's clinical condition and the possible return of disease activity after stopping the medicinal product.

Breast-feeding

Natalizumab is excreted in human milk. The effect of natalizumab on newborn/infants is unknown. Breast-feeding should be discontinued during treatment with TYSABRI.

Fertility

Reductions in female guinea pig fertility were observed in one study at doses in excess of the human dose; natalizumab did not affect male fertility.
It is considered unlikely that natalizumab will affect fertility performance in humans following the maximum recommended dose.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed with TYSABRI. However, given that dizziness has been commonly reported, patients who experience this adverse reaction should be advised not to drive or use machines until it has resolved.

4.8 Undesirable effects

Summary of the safety profile

In placebo-controlled trials in 1,617 MS patients treated with natalizumab for up to 2 years (placebo: 1,135), adverse events leading to discontinuation of therapy occurred in 5.8% of patients treated with natalizumab (placebo: 4.8%). Over the 2-year duration of the studies, 43.5% of patients treated with natalizumab reported adverse reactions (placebo: 39.6%).

The highest incidence of adverse reactions identified from placebo-controlled trials in multiple sclerosis patients with natalizumab given at the recommended dose, are reported as dizziness, nausea, urticaria and rigors associated with infusions.

Tabulated list of adverse reactions

Adverse reactions reported with natalizumab with an incidence of 0.5% greater than reported with placebo are shown below.

The reactions are reported as MedDRA preferred terms under the MedDRA primary system organ class. Frequencies were defined as follows:

Common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

MedDRA System Organ Class	Adverse reaction	Frequency category
Infections and infestations	Urinary tract infection	Common
	Nasopharyngitis	Common
Immune system disorders	Urticaria	Common
	Hypersensitivity	Uncommon
Nervous system disorders	Headache	Common
	Dizziness	Common
	Progressive Multifocal Leukoencephalopathy (PML)	Uncommon
Gastrointestinal disorders	Vomiting	Common
	Nausea	Common
Musculoskeletal and connective tissue disorders	Arthralgia	Common
General disorders and administration site conditions	Rigors	Common
	Pyrexia	Common
	Fatigue	Common

Description of selected adverse reactions

Infusion reactions

In 2-year controlled clinical trials in MS patients, an infusion-related event was defined as an adverse event occurring during the infusion or within 1 hour of the completion of the infusion. These occurred in 23.1% of MS patients treated with natalizumab (placebo: 18.7%). Events reported more commonly with natalizumab than with placebo included dizziness, nausea, urticaria and rigors.

Hypersensitivity reactions

In 2-year controlled clinical trials in MS patients, hypersensitivity reactions occurred in up to 4% of patients. Anaphylactic/anaphylactoid reactions occurred in less than 1% of patients receiving TYSABRI. Hypersensitivity reactions usually occurred during the infusion or within the 1-hour period after the completion of the infusion (See section 4.4). In post-marketing experience, there have been reports of hypersensitivity reactions which have occurred with one or more of the following associated symptoms: hypotension, hypertension, chest pain, chest discomfort, dyspnoea, angioedema, in addition to more usual symptoms such as rash and urticaria.

Immunogenicity

In 10% of patients antibodies against natalizumab were detected in 2-year controlled clinical trials in MS patients. Persistent anti-natalizumab antibodies (one positive test reproducible on retesting at least 6 weeks later) developed in approximately 6% of patients. Antibodies were detected on only one occasion in an additional 4% of patients. Persistent antibodies were associated with a substantial decrease in the effectiveness of

TYSABRI and an increased incidence of hypersensitivity reactions. Additional infusion-related reactions associated with persistent antibodies included rigors, nausea, vomiting and flushing (see section 4.4).

If, after approximately 6 months of therapy, persistent antibodies are suspected, either due to reduced efficacy or due to occurrence of infusion-related events, they may be detected and confirmed with a subsequent test 6 weeks after the first positive test. Given that efficacy may be reduced or the incidence of hypersensitivity or infusion-related reactions may be increased in a patient with persistent antibodies, treatment should be discontinued in patients who develop persistent antibodies.

Infections, including PML and opportunistic infections

In 2-year controlled clinical trials in MS patients, the rate of infection was approximately 1.5 per patient-year in both natalizumab- and placebo-treated patients. The nature of the infections was generally similar in natalizumab- and placebo-treated patients. A case of *cryptosporidium* diarrhoea was reported in MS clinical trials. In other clinical trials, cases of additional opportunistic infections have been reported, some of which were fatal. The majority of patients did not interrupt natalizumab therapy during infections and recovery occurred with appropriate treatment.

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 TYSABRI. The duration of treatment with TYSABRI prior to onset ranged from a few months to several years (see section 4.4).

In postmarketing experience, rare cases of ARN have been observed in patients receiving TYSABRI. Some cases have occurred in patients with central nervous system (CNS) herpes infections (e.g. herpes meningitis and encephalitis). Serious cases of ARN, either affecting one or both eyes, led to blindness in some patients. The treatment reported in these cases included anti-viral therapy and in some cases, surgery (see section 4.4).

Cases of PML have been reported from clinical trials, post-marketing observational studies and post-marketing passive surveillance. PML usually leads to severe disability or death (see section 4.4). Cases of JCV GCN have also been reported during postmarketing use of TYSABRI. Symptoms of JCV GCN are similar to PML.

Hepatic events

Spontaneous cases of serious liver injuries, increased liver enzymes, hyperbilirubinaemia have been reported during the post marketing phase (see section 4.4).

Anaemia and haemolytic anaemia

Rare, serious cases of anaemia and haemolytic anaemia have been reported in patients treated with TYSABRI in post-marketing observational studies.

Malignancies

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. See section 4.3.

Effects on laboratory tests

In 2-year controlled clinical trials in MS patients TYSABRI treatment was associated with increases in circulating lymphocytes, monocytes, eosinophils, basophils and nucleated red blood cells. Elevations in neutrophils were not seen. Increases from baseline for lymphocytes, monocytes, eosinophils and basophils ranged from 35% to 140% for individual cell types but mean cell counts remained within normal ranges. During treatment with TYSABRI, small reductions in haemoglobin (mean decrease 0.6 g/dl), haematocrit (mean decrease 2%) and red blood cell counts (mean decrease 0.1 x 10^6/l) were seen. All changes in haematological variables returned to pre-treatment values, usually within 16 weeks of last dose of the medicinal product and the changes were not associated with clinical symptoms. In post-marketing experience, there have also been reports of eosinophilia (eosinophil count >1,500/mm^3) without clinical symptoms. In such cases where TYSABRI therapy was discontinued the elevated eosinophil levels resolved.

Paediatric population

Serious adverse events were evaluated in 621 MS paediatric patients included in a meta-analysis (see also Section 5.1). Within the limitations of these data, there were no new safety signals identified in this patient population. 1 case of herpes meningitis was reported in the meta-analysis. No cases of PML were identified in the meta-analysis, however, PML has been reported in natalizumab treated paediatric patients in the post-marketing setting.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions:

Ireland
HPRA Pharmacovigilance
Website: www.hpra.ie

Malta
ADR Reporting
Website: www.medicinesauthority.gov.mt/adrportal

United Kingdom
Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store

4.9 Overdose

No case of overdose has been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Selective immunosuppressive agents, ATC code: L04AA23

Pharmacodynamic effects

Natalizumab is a selective adhesion-molecule inhibitor and binds to the α4-subunit of human integrins, which is highly expressed on the surface of all leukocytes, with the exception of neutrophils. Specifically, natalizumab binds to the α4β1 integrin, blocking the interaction with its cognate receptor, vascular cell adhesion molecule-1 (VCAM-1), and ligands osteopontin, and an alternatively spliced domain of fibronectin, connecting segment-1 (CS-1). Natalizumab blocks the interaction of α4β7 integrin with the mucosal addressin cell adhesion molecule-1 (MadCAM-1). Disruption of these molecular interactions prevents transmigration of mononuclear leukocytes across the endothelium into inflamed parenchymal tissue. A further mechanism of action of natalizumab may be to suppress ongoing inflammatory reactions in diseased tissues by inhibiting the interaction of α4-expressing leukocytes with their ligands in the extracellular matrix and on parenchymal cells. As such, natalizumab may act to suppress inflammatory activity present at the disease site, and inhibit further recruitment of immune cells into inflamed tissues.

In MS, lesions are believed to occur when activated T-lymphocytes cross the blood-brain barrier (BBB). Leukocyte migration across the BBB involves interaction between adhesion molecules on inflammatory cells and endothelial cells of the vessel wall. The interaction between α4β1 and its targets is an important component of pathological inflammation in the brain and disruption of these interactions leads to reduced inflammation. Under normal conditions, VCAM-1 is not expressed in the brain parenchyma. However, in the presence of pro-inflammatory cytokines, VCAM-1 is upregulated on endothelial cells and possibly on glial cells near the sites of inflammation. In the setting of central nervous system (CNS) inflammation in MS, it is the interaction of α4β1 with VCAM-1, CS-1 and osteopontin that mediates the firm adhesion and transmigration of leukocytes into the brain parenchyma and may perpetuate the inflammatory cascade in CNS tissue. Blockade of the molecular interactions of α4β1 with its targets reduces inflammatory activity present in the brain in MS and inhibits further recruitment of immune cells into inflamed tissue, thus reducing the formation or enlargement of MS lesions.

Clinical efficacy

Efficacy as monotherapy has been evaluated in one randomised, double-blind, placebo-controlled study lasting 2 years (AFFIRM study) in relapsing-remitting MS patients who had experienced at least 1 clinical relapse during the year prior to entry

and had a Kurtzke Expanded Disability Status Scale (EDSS) score between 0 and 5. Median age was 37 years, with a median disease duration of 5 years. The patients were randomised with a 2:1 ratio to receive TYSABRI 300 mg (n = 627) or placebo (n = 315) every 4 weeks for up to 30 infusions. Neurological evaluations were performed every 12 weeks and at times of suspected relapse. MRI evaluations for T1-weighted gadolinium (Gd)-enhancing lesions and T2-hyperintense lesions were performed annually.

Study features and results are presented in the table below.

AFFIRM study: Main features and results		
Design	Monotherapy; randomised double-blind placebo-controlled parallel-group trial for 120 weeks	
Subjects	RRMS (McDonald criteria)	
Treatment	Placebo / Natalizumab 300 mg i.v. every 4 weeks	
One year endpoint	Relapse rate	
Two year endpoint	Progression on EDSS	
Secondary endpoints	Relapse rate derived variables / MRI-derived variables	
Subjects	Placebo	Natalizumab
Randomised	315	627
Completing 1 years	296	609
Completing 2 years	285	589
Age yrs, median (range)	37 (19-50)	36 (18-50)
MS-history yrs, median (range)	6.0 (0-33)	5.0 (0-34)
Time since diagnosis, yrs median (range)	2.0 (0-23)	2.0 (0-24)
Relapses in previous 12 months, median (range)	1.0 (0-5)	1.0 (0-12)
EDSS-baseline, median (range)	2 (0-6.0)	2 (0-6.0)
RESULTS		
Annual relapse rate		
After one year (primary endpoint)	0.805	0.261
After two years	0.733	0.235
One year	Rate ratio 0.33 $CI_{95\%}$ 0.26 ; 0.41	
Two years	Rate ratio 0.32 $CI_{95\%}$ 0.26 ; 0.40	
Relapse free		
After one year	53%	76%
After two years	41%	67%
Disability		

Proportion progressed[1](12-week confirmation; primary outcome)	29%	17%
	Hazard ratio 0.58, $CI_{95\%}$ 0.43; 0.73, p<0.001	
Proportion progressed[1](24-week confirmation)	23%	11%
	Hazard ratio 0.46, $CI_{95\%}$ 0.33; 0.64, p<0.001	
MRI (0-2 years)		
Median % change in T2-hyperintense lesion volume	+8.8%	-9.4% (p<0.001)
Mean number of new or newly-enlarging T2-hyperintense lesions	11.0	1.9 (p<0.001)
Mean number of T1-hypointense lesions	4.6	1.1 (p<0.001)
Mean number of Gd-enhancing lesions	1.2	0.1 (p<0.001)

[1] Progression of disability was defined as at least a 1.0 point increase on the EDSS from a baseline EDSS >=1.0 sustained for 12 or 24 weeks or at least a 1.5 point increase on the EDSS from a baseline EDSS =0 sustained for 12 or 24 weeks.

In the sub-group of patients indicated for treatment of rapidly evolving relapsing remitting MS (patients with 2 or more relapses and 1 or more Gd+ lesion), the annualised relapse rate was 0.282 in the TYSABRI treated group (n = 148) and 1.455 in the placebo group (n = 61) (p <0.001). Hazard ratio for disability progression was 0.36 (95% CI: 0.17, 0.76) p = 0.008. These results were obtained from a *post hoc* analysis and should be interpreted cautiously. No information on the severity of the relapses before inclusion of patients in the study is available.

Interim analysis of results (as of May 2015) from the ongoing TYSABRI Observational Program (TOP), a phase 4, multicentre, single-arm study (n=5770) demonstrated that patients switching from beta interferon (n= 3255) or glatiramer acetate (n= 1384) to TYSABRI showed a sustained, significant decrease in annualised relapse rate (p< 0.0001). Mean EDSS scores remained stable over 5 years. Consistent with efficacy results observed for patients switching from beta interferon or glatiramer acetate to TYSABRI, for patients switching from fingolimod (n=147) to TYSABRI, a significant decrease in annualised relapse rate (ARR) was observed, which remained stable over 2 years, and mean EDSS scores remained similar from baseline to Year 2. The limited sample size and shorter duration of TYSABRI exposure for this subgroup of patients should be considered when interpreting these data.

A post-marketing meta-analysis was conducted using data from 621 paediatric MS patients treated with TYSABRI (median age 17 years, range was 7-18 years, 91% aged ≥14 years). Within this analysis, a limited subset of patients with data available prior to treatment (158 of the 621 patients) demonstrated a reduction in ARR from 1.466 (95% CI 1.337, 1.604) prior to treatment to 0.110 (95% CI 0.094, 0.128).

In a pre-specified, retrospective analysis of US anti-JCV antibody positive TYSABRI patients (TOUCH registry), the risk of PML was compared between patients treated

with the approved dosing interval and patients treated with extended interval dosing as identified in the last 18 months of exposure (EID, average dosing intervals of approximately 6 weeks). The majority (85%) of patients dosed with EID had received the approved dosing for ≥1 year prior to switching to EID. The interim analysis showed a lower risk of PML in patients treated with EID (hazard ratio = 0.06 95% CI of hazard ratio = 0.01- 0.22). The efficacy of TYSABRI when administered with EID has not been established, and therefore the benefit/risk balance of EID is unknown (see section 4.4).

Efficacy has been modelled for patients who switch to longer dosing after ≥1 year of approved TYSABRI dosing and who did not experience a relapse in the year prior to switching. Current pharmacokinetic/pharmacodynamic statistical modelling and simulation indicate that the risk of MS disease activity for patients switching to longer dosing intervals may be higher for patients with body weight >80kg or those with dosing intervals ≥7 weeks. No prospective clinical studies have been completed to validate these findings.

5.2 Pharmacokinetic properties

Following the repeat intravenous administration of a 300 mg dose of natalizumab to MS patients, the mean maximum observed serum concentration was 110 ± 52 μg/ml. Mean average steady-state trough natalizumab concentrations over the dosing period ranged from 23 μg/ml to 29 μg/ml. The predicted time to steady-state was approximately 36 weeks.

A population pharmacokinetics analysis was conducted on samples from over 1,100 MS patients receiving doses ranging from 3 to 6 mg/kg natalizumab. Of these, 581 patients received a fixed 300 mg dose as monotherapy. The mean ± SD steady-state clearance was 13.1 ± 5.0 ml/h, with a mean ± SD half-life of 16 ± 4 days. The analysis explored the effects of selected covariates including body weight, age, gender, hepatic and renal function, and presence of anti-natalizumab antibodies upon pharmacokinetics. Only body weight and the presence of anti-natalizumab antibodies were found to influence natalizumab disposition. Body weight was found to influence clearance in a less-than-proportional manner, such that a 43% change in body weight resulted in a 31% to 34% change in clearance. The change in clearance was not clinically significant. The presence of persistent anti-natalizumab antibodies increased natalizumab clearance approximately 3-fold, consistent with reduced serum natalizumab concentrations observed in persistently antibody-positive patients**,** (see section 4.8).

The pharmacokinetics of natalizumab in paediatric MS patients has not been established. The pharmacokinetics of natalizumab in patients with renal or hepatic insufficiency has not been studied.

The effect of plasma exchange on natalizumab clearance and pharmacodynamics was evaluated in a study of 12 MS patients. Estimates of the total natalizumab removal after 3 plasma exchanges (over a 5-8 day interval) was approximately 70-80%. This compares to approximately 40% seen in earlier studies in which measurements occurred after natalizumab discontinuation over a similar period of observation. The

impact of plasma exchange on the restitution of lymphocyte migration and ultimately its clinical usefulness is unknown.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity.

Consistent with the pharmacological activity of natalizumab, altered trafficking of lymphocytes was seen as white blood cell increases as well as increased spleen weights in most *in vivo* studies. These changes were reversible and did not appear to have any adverse toxicological consequences.

In studies conducted in mice, growth and metastasis of melanoma and lymphoblastic leukaemia tumour cells was not increased by the administration of natalizumab.

No clastogenic or mutagenic effects of natalizumab were observed in the Ames or human chromosomal aberration assays. Natalizumab showed no effects on *in vitro* assays of α4-integrin-positive tumour line proliferation or cytotoxicity.

Reductions in female guinea pig fertility were observed in one study at doses in excess of the human dose; natalizumab did not affect male fertility.

The effect of natalizumab on reproduction was evaluated in 5 studies, 3 in guinea pigs and 2 in *cynomolgus* monkeys. These studies showed no evidence of teratogenic effects or effects on growth of offspring. In one study in guinea pigs, a small reduction in pup survival was noted. In a study in monkeys, the number of abortions was doubled in the natalizumab 30 mg/kg treatment groups versus matching control groups. This was the result of a high incidence of abortions in treated groups in the first cohort that was not observed in the second cohort. No effects on abortion rates were noted in any other study. A study in pregnant *cynomolgus* monkeys demonstrated natalizumab-related changes in the foetus that included mild anaemia, reduced platelet counts, increased spleen weights and reduced liver and thymus weights. These changes were associated with increased splenic extramedullary haematopoiesis, thymic atrophy and decreased hepatic haematopoiesis. Platelet counts were also reduced in offspring born to mothers treated with natalizumab until parturition, however there was no evidence of anaemia in these offspring. All changes were observed at doses in excess of the human dose and were reversed upon clearance of natalizumab.

In *cynomolgus* monkeys treated with natalizumab until parturition, low levels of natalizumab were detected in the breast milk of some animals.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium phosphate, monobasic, monohydrate
Sodium phosphate, dibasic, heptahydrate
Sodium chloride

Polysorbate 80 (E433)
Water for injections

6.2 Incompatibilities

TYSABRI must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial
4 years

Diluted solution

After dilution with sodium chloride 9 mg/ml (0.9%) solution for injection, immediate use is recommended. If not used immediately, the diluted solution must be stored at 2˚C - 8˚C and infused within 8 hours of dilution. In-use storage times and conditions prior to use are the responsibility of the user.

6.4 Special precautions for storage

Store in a refrigerator (2˚C - 8˚C).
Do not freeze.
Keep the vial in the outer carton in order to protect from light.

For storage conditions after dilution of the medicinal product see section 6.3.

6.5 Nature and contents of container

15 ml concentrate in a vial (type I glass) with a stopper (chlorobutyl rubber) and a seal (aluminium) with a flip-off cap.
Pack size of one vial per carton.

6.6 Special precautions for disposal and other handling

Instructions for use:

- Inspect the TYSABRI vial for particles prior to dilution and administration. If particles are observed and/or the liquid in the vial is not colourless, clear to slightly opalescent, the vial must not be used.

- Use aseptic technique when preparing TYSABRI solution for intravenous (IV) infusion. Remove flip-off cap from the vial. Insert the syringe needle into the vial through the centre of the rubber stopper and remove 15 ml concentrate for solution for infusion.

- Add the 15 ml concentrate for solution for infusion to 100 ml sodium chloride 9 mg/ml (0.9%) solution for injection. Gently invert the TYSABRI solution to mix completely. Do not shake.

- TYSABRI must not be mixed with other medicinal products or diluents.
- Visually inspect the diluted medicinal product for particles or discolouration prior to administration. Do not use if it is discoloured or if foreign particles are seen.
- The diluted medicinal product is to be used as soon as possible and within 8 hours of dilution. If the diluted medicinal product is stored at 2˚C - 8˚C (do not freeze), allow the solution to warm to room temperature prior to infusion.
- The diluted solution is to be infused intravenously over 1 hour at a rate of approximately 2 ml/minute.
- After the infusion is complete, flush the intravenous line with sodium chloride 9 mg/ml (0.9%) solution for injection.
- Each vial is for single–use only.
- Any unused medicinal product or waste material must be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Biogen Netherlands B.V.
Prins Mauritslaan 13
1171 LP Badhoevedorp
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/346/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27th June 2006
Date of latest renewal: 18th April 2016

10. DATE OF REVISION OF THE TEXT

10/2019

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

5.5 *Appendix 2. Package Leaflet (PL)*

Package leaflet: Information for the patient

TYSABRI 300 mg concentrate for solution for infusion
natalizumab

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

In addition to this leaflet you will be given a Patient Alert Card, which contains important safety information that you need to know before you are given TYSABRI (pronounced tie-SA-bree) and during treatment with TYSABRI.

- Keep this leaflet and the Patient Alert Card. You may need to read them again. Keep the leaflet and Alert Card with you during treatment and for six months after the last dose of TYSABRI, since side effects may occur even after you have stopped treatment.
- If you have any further questions, ask your doctor.
- If you get any side effects talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What TYSABRI is and what it is used for

TYSABRI contains the active substance (natalizumab). This active ingredient is called a monoclonal antibody. These antibodies work by binding to proteins in the body so that the harmful effect of that protein is removed.

TYSABRI is used to treat multiple sclerosis (MS). MS causes inflammation in the brain that damages the nerve cells. TYSABRI stops the cells that cause inflammation from going into your brain. This reduces nerve damage caused by MS.

What are the symptoms of multiple sclerosis?
The symptoms of MS vary from patient to patient, and you may experience some or none of them.

Symptoms can include; walking problems, numbness in the face, arms or legs, problems seeing things, tiredness, feeling off-balance or light headed, bladder and bowel problems, difficulty in thinking and concentrating, depression, acute or chronic pain, sexual problems, and stiffness and muscle spasms. When the symptoms flare up, it is called a relapse (also known as an exacerbation or an attack). When a relapse occurs, you may notice the symptoms suddenly, within a few hours, or slowly progressing over several days. Your symptoms will then usually improve gradually (this is called a remission).

In clinical trials, TYSABRI approximately halved the progression of the disabling effects of MS and also decreased the number of MS attacks by about two-thirds. When you receive TYSABRI you might not notice any improvement, but TYSABRI may still be working to prevent your MS becoming worse.

2. What you need to know before you use TYSABRI

Before you start treatment with TYSABRI, it is important that you and your doctor have discussed the benefits you would expect to receive from this treatment and the risks that are associated with it.

Do not use TYSABRI

- If you are allergic to natalizumab or any of the other ingredients of this medicine (listed in section 6).

- If your doctor has told you that you have PML (progressive multifocal leukoencephalopathy). PML is a rare infection of the brain.

- If your doctor tells you that you have a serious problem with your immune system (due to disease for example, HIV or due to a medicine you are taking or have previously taken

- If you are taking medicines that suppress or modulate the immune system including other medicines used to treat MS disease. These medicines cannot be used with TYSABRI (see Using other medicines, below).

- If you have an active cancer (unless it is a type of skin cancer called basal cell carcinoma).

Warnings and precautions

Talk to your doctor before using TYSABRI.

Infections

Tell your doctor **immediately** if you have, or think you have, any sort of infection (see side effects). Some infections other than PML may also be serious and can be due to viruses, bacteria, or other causes.

There have been cases of a rare brain infection called PML (progressive multifocal leukoencephalopathy) that have occurred in patients who have been given TYSABRI. PML may lead to severe disability or death.

- The symptoms of PML may be similar to an MS relapse (e.g. weakness or visual changes). Therefore, if you believe your MS is getting worse or if you notice any new symptoms while you are on TYSABRI treatment or for up to 6 months after stopping TYSABRI treatment, it is very important that you speak to your doctor as soon as possible.

- Speak with your partner or caregivers and inform them about your treatment. Symptoms might arise that you might not become aware of by yourself, such as changes in mood or behaviour, memory lapses, speech and communication difficulties, which your doctor may need to investigate further to rule out PML. You should remain aware for symptoms that might arise for up to 6 months after stopping TYSABRI treatment.

- You will also find this information in the Patient Alert Card you have been given by your doctor. It is important that you keep this Alert Card and show it to your partner or caregivers.

PML is associated with an uncontrolled increase of the JC virus in the brain, although the reason for this increase in some patients treated with TYSABRI is unknown. 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. JC virus is a common virus which infects many people but does not normally cause noticeable illness.

Your doctor may test your blood to check if you have antibodies to the JC virus before you start treatment with TYSABRI. These antibodies are a sign that you have been infected by JC virus. Your doctor may repeat this blood test while you are on TYSABRI treatment to check if anything has changed.

The risk of PML with TYSABRI is higher:

- If you have antibodies to the JC virus in your blood.
- The longer that you are on treatment especially if you have been on treatment for more than two years.
- If you have previously taken a medicine called an immunosuppressant. These medicines reduce the activity of your body's immune system.

If you have all three risks described above your chance of getting PML is higher.

If you have previously not been treated with immunosuppressants and have received TYSABRI for 2 years or longer, the level of your anti-JCV antibody response may be associated with the risk of getting PML.

For those with a lower risk of PML, your doctor may repeat the test regularly to check if anything has changed if:

- If you do not have antibodies to the JC virus in your blood OR

- If you have been treated for more than 2 years and you have a lower level of JCV antibodies in your blood.

You should discuss with your doctor if TYSABRI is the most suitable treatment for you before you start taking TYSABRI and when you have been taking TYSABRI for more than two years.

In patients with PML a reaction known as IRIS (Immune Reconstitution Inflammatory Syndrome) is likely to occur after treatment for PML, as TYSABRI is removed from your body. IRIS may lead to your condition getting worse, including worsening of brain function.

Allergic reactions
A few patients have had an allergic reaction to TYSABRI. Your doctor will check for allergic reactions during the infusion and for 1 hour afterwards.

Will TYSABRI always work?
In a few patients who use TYSABRI, over time the body's natural defence may stop TYSABRI from working properly (the body develops antibodies to TYSABRI). Your doctor can decide whether TYSABRI is not working properly for you by testing your blood and will stop TYSABRI, if necessary.

Other medicines and TYSABRI
Tell your doctor if you are taking or have recently taken or might take any other medicines.

- You **must not** use TYSABRI if you are being treated with other medicines to treat your MS disease

- You may not be able to use TYSABRI if you are currently receiving or have previously received medicines that affect your immune system

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine

- Do not use TYSABRI if you are pregnant unless you have discussed this with your doctor. Be sure to tell your doctor immediately if you are pregnant, think you may be pregnant, or if you are planning to become pregnant.

- Do not breast-feed whilst using TYSABRI. You should discuss with your doctor whether you choose to breast-feed or to use TYSABRI.

Driving and using machines
There are no studies on the effects of TYSABRI on the ability to drive and use machines. However, if you experience dizziness, a common side effect, then you should not drive or use machines.

TYSABRI contains sodium

Each vial of TYSABRI contains 2.3 mmol (or 52 mg) of sodium. After dilution for use, this medicinal product contains 17.7 mmol (or 406 mg) sodium per dose. This should be considered if you are on a controlled sodium diet.

3. How to use TYSABRI

TYSABRI will be given to you by a doctor experienced in the treatment of MS. Your doctor may switch you directly from another medicine for MS to TYSABRI if there are no signs of abnormalities caused by your previous treatment. Your doctor should do a blood test in order to test for abnormalities and whether you have antibodies to the JC virus. To switch from some MS medicines, your doctor may advise you to wait for a certain time to ensure that most of the previous medicine has left your body. Initiating treatment with TYSABRI after alemtuzumab is generally not recommended. If you have been treated with alemtuzumab, a thorough evaluation and discussion with your doctor is required to decide if a switch to TYSABRI is appropriate for you.

Always use this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

- The recommended dose for adults is 300 mg given once every 4 weeks.
- TYSABRI must be diluted before it is given to you. It is given as a drip into a vein (by intravenous infusion), usually in your arm. This takes about 1 hour.
- Information for medical or healthcare professionals on how to prepare and administer TYSABRI is provided at the end of this leaflet.
- It is important to continue with your medicine for as long as you and your doctor decide that it is helping you. Continuous dosing with TYSABRI is important, especially during the first few months of treatment. This is because patients who received one or two doses of TYSABRI and then had a gap in treatment of three months or more, were more likely to have an allergic reaction when resuming treatment.

If you miss your dose of TYSABRI
If you miss your usual dose of TYSABRI, arrange with your doctor to receive it as soon as you can. You can then continue to receive your dose of TYSABRI every 4 weeks.

Always use this medicine exactly as described in this leaflet or as your doctor has told you. Check with your doctor if you are not sure.

If you have any further questions on TYSABRI, ask your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Speak to your doctor or nurse immediately if you notice any of the following

Symptoms of serious infections including:
– An unexplained fever
– Severe diarrhoea
– Shortness of breath
– Prolonged dizziness
– Headache
– Weight loss
– Listlessness
– Impaired vision
– Pain or redness of the eye(s)

A group of symptoms caused by a serious infection of the brain including:
– Changes in personality and behaviour such as confusion, delirium or loss of consciousness, seizures (fits), headache, nausea / vomiting, stiff neck, extreme sensitivity to bright light, fever, rash (anywhere on the body).

These symptoms may be caused by an infection of the brain (*encephalitis*) or its covering layer (*meningitis*).

Signs of allergy to TYSABRI, during or shortly after your infusion:
- Itchy rash (hives)
- Swelling of your face, lips or tongue
- Difficulty breathing
- Chest pain or discomfort
- Increase or decrease in your blood pressure (your doctor or nurse will notice this if they are monitoring your blood pressure).

Signs of a possible liver problem:
- Yellowing of your skin or the whites of your eyes
- Unusual darkening of the urine.

TYSABRI can also have other side effects.

Side effects are listed below by how commonly they have been reported in clinical trials:

Common side effects that may affect up to 1 in 10 people:
- Urinary tract infection
- Sore throat and runny or blocked up nose
- Shivering
- Itchy rash (hives)
- Headache
- Dizziness
- Feeling sick (nausea)
- Being sick (vomiting)
- Joint pain

- Fever
- Tiredness

Uncommon side effects that may affect up to 1 in 100 people:
- Severe allergy (hypersensitivity)
- Progressive multifocal leukoencephalopathy (PML)

Rare side effects that may affect up to 1 in 1,000 people:
- Unusual infections (so-called "Opportunistic infections")
- Severe anaemia (decrease in your red blood cells which can make your skin pale and can make you feel breathless or lacking energy)

Speak to your doctor as soon as possible if you think you have an infection.
Show the Alert Card and this package leaflet to any doctor involved with your treatment, not only to your neurologist.

You will also find this information in the Patient Alert Card you have been given by your doctor.

Reporting of side effects
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via:

Ireland
HPRA Pharmacovigilance
Website: www.hpra.ie

Malta
ADR Reporting
Website: www.medicinesauthority.gov.mt/adrportal

United Kingdom
Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store

By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store TYSABRI

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date stated on the label and carton. The expiry date refers to the last day of that month.

Unopened vial:
Store in a refrigerator (2°C to 8°C).
Do not freeze.
Keep the vial in the outer carton in order to protect from light.

Diluted solution:
After dilution, immediate use is recommended. If not used immediately, the diluted solution must be stored at 2˚C - 8˚C and infused within 8 hours of dilution.

Do not use this medicine if you notice particles in the liquid and/or the liquid in the vial is discoloured.

6. Contents of the pack and other information

What TYSABRI contains
The active substance is natalizumab. Each 15 ml vial of concentrate contains 300 mg natalizumab (20 mg/ml). When diluted, the solution for infusion contains approximately 2.6 mg/ml of natalizumab.

The other ingredients are:
Sodium phosphate, monobasic, monohydrate,
Sodium phosphate, dibasic, heptahydrate,
Sodium chloride (see section 2 'TYSABRI contains sodium'),
Polysorbate 80 (E433)
Water for injections

What TYSABRI looks like and contents of the pack
TYSABRI is a clear, colourless to slightly cloudy liquid.
Each carton contains one glass vial.

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Manufacturer
Biogen (Denmark) Manufacturing ApS
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For any further information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

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This leaflet was last revised in 10/2019

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

The following information is intended for healthcare professionals only:

1. Inspect the TYSABRI vial for particles prior to dilution and administration. If particles are observed and/or the liquid in the vial is not colourless, clear to slightly opalescent, the vial must not be used.

2. Use aseptic technique when preparing TYSABRI solution for intravenous infusion. Remove flip-top from the vial. Insert the syringe needle into the vial through the centre of the rubber stopper and remove 15 ml concentrate for solution for infusion.

3. Add the 15 ml concentrate for solution for infusion to 100 ml sodium chloride 9 mg/ml (0.9%) solution for injection. Gently invert the TYSABRI solution to mix completely. Do not shake.

4. TYSABRI must not be mixed with other medicinal products or diluents.

5. Visually inspect the diluted medicinal product for particles or discolouration prior to administration. Do not use if it is discoloured or if foreign particles are seen.

6. The diluted medicinal product is to be used as soon as possible and within 8 hours of dilution. If the diluted medicinal product is stored at 2°C - 8°C (do not freeze), allow the solution to warm to room temperature prior to infusion.

7. The diluted solution is to be infused intravenously over 1 hour at a rate of approximately 2 ml/minute.

8. After the infusion is complete, flush the intravenous line with sodium chloride 9 mg/ml (0.9%) solution for injection.

9. Each vial is for single–use only.

10. In order to improve traceability of biological medicinal products, the product name (Tysabri) and batch number of the administered product should be clearly recorded.

11. Any unused medicinal product or waste material must be disposed of in accordance with local requirements.

5.6

5.7 *Appendix 3. Patient Alert Card*

TYSABRI Patient Alert Card	**During treatment with TYSABRI**
Patient's Name:_____ Doctor's Name:_____ Doctor's Phone: _____ Date TYSABRI Started: _____ This alert card contains important safety information that you need to be aware of **before, during** and **after stopping** treatment with TYSABRI.	**Progressive Multifocal Leukoencephalopathy (PML)** PML, a rare brain infection, has occurred in patients who have been given TYSABRI. PML usually leads to severe disability or death. The risk of PML appears to increase with treatment duration, especially beyond 2 years. The symptoms of PML may be similar to an MS relapse. Therefore, if you believe your MS is getting worse or if you notice any new symptoms while you are on TYSABRI treatment or for up to 6 months

• Show this card to any doctor involved with your treatment, not only to your neurologist. • Please read the TYSABRI "Package Leaflet" carefully before you start using this medicine. • Keep this card with you for 6 months after the last dose of TYSABRI, since side effects may occur even after you have stopped treatment with TYSABRI. • Show this card to your partner or caregivers. They might see symptoms of PML that you might not notice, such as changes in mood or behaviour, memory lapses, speech and communication difficulties. You should remain aware for symptoms that might arise for up to 6 months after stopping TYSABRI treatment. **<u>Prior to treatment with TYSABRI</u>** • You should not be treated with TYSABRI if you have a serious problem with your immune system • You should not take any other long-term medicines for your multiple sclerosis while receiving TYSABRI	after stopping TYSABRI treatment, it is very important that you speak to your doctor as soon as possible. PML symptoms generally develop more slowly than those associated with an MS relapse (over days or weeks), and may be similar to your MS symptoms. Signs include: o changes in mental ability and concentration, o behavioural changes, o weakness on one side of the body, o vision problems, o new neurological symptoms that are unusual for you. Management of PML requires withdrawal or removal of TYSABRI from the blood, usually by 'plasma exchange'. In patients with PML a severe inflammatory reaction known as IRIS is likely to occur within days to a few weeks after treatment for PML (and removal of TYSABRI). IRIS may lead to a variety of symptoms, including worsening of brain (neurological) function. **Serious Infections** Other serious infections may occur with TYSABRI. Speak to your doctor as soon as possible if you think you have developed a severe, persistent infection, for example a persistent fever. **<u>Approved [02/2016]</u>**

5.8

5.9 *Appendix 4. Treatment Initiation Form, Treatment Continuation Form, and Treatment Discontinuation Form*

TYSABRI Treatment Initiation Form
TYSABRI (Natalizumab) 300 mg concentrate solution for infusion

This form should be read carefully before starting treatment with TYSABRI. Please follow the advice in this form to ensure that you are fully informed of, and understand the risk of PML (progressive multifocal leukoencephalopathy), IRIS (Immune reconstitution Inflammatory Disease) and other important adverse effects of TYSABRI

Before starting treatment with TYSABRI you should:
- **read the Package Leaflet which is included in each box of TYSABRI;**
- **read the Alert Card given to you by your doctor;**
- **discuss with your doctor the benefits and the risks associated with this treatment.**

The Package Leaflet and the Alert Card contain important safety information about PML, a rare brain infection that has occurred in patients who have been given TYSABRI, and which may lead to severe disability or death.

JC virus is a common virus which infects many people but does not normally cause noticeable illness. PML is associated with an uncontrolled increase of the JC virus in the brain, although the reason for this increase in some patients treated with TYSABRI is unknown.

The risk of PML with TYSABRI is higher

- If you have antibodies to the JC virus in your blood.
- The longer that you are on treatment with TYSABRI, especially if you have been on treatment for more than two years
- If you have taken an immunosuppressant (a medicine that reduces the activity of your body's immune system) at any time before starting TYSABRI treatment.

Your doctor should discuss the potential risk of developing PML with you before you start treatment with TYSABRI**.**

Your doctor may test your blood to check if you have antibodies to the JC virus before you start treatment with TYSABRI. Your doctor may repeat the test while you are on TYSABRI treatment to check if anything has changed. The risk of PML is higher if you have all the risk factors described above, or if you have not taken an immunosuppressant medication prior to starting TYSABRI and have higher levels of antibodies to the JC virus and you have been on TYSABRI for more than 2 years. Your doctor will monitor you more closely if you are at higher risk for PML.

You should discuss with your doctor if TYSABRI is the most suitable treatment for you before you start taking TYSABRI and when you have been taking TYSABRI for more than two years.

In patients with PML, a reaction known as IRIS (Immune Reconstitution Inflammatory Syndrome) is likely to occur after treatment for PML, as TYSABRI is removed from your body. IRIS may lead to your condition getting worse, including worsening of brain function.

The Package Leaflet should be read each time that you take TYSABRI because it may have new information that is important to your treatment.

You should keep the Alert Card with you to remind you of the important safety information, in particular any symptoms you may develop which could possibly indicate PML, if appropriate, you should show the Alert Card to your partner or caregiver.

If you do not have the Package Leaflet or the Alert Card then please ask your doctor to provide them to you before you receive your infusion of TYSABRI.

[*Patient's name, signature and date of signature, and Doctor's name, signature and date of signature*].

PML risk estimate:

Patients who are anti-JCV antibody negative

Based on global data, if you do not have antibodies to JCV your chance of getting PML is 0.1/1000 (or 1 in 10,000) patients.

Patients who are anti-JCV antibody positive

If you do have antibodies to JCV, your risk of developing PML will vary depending on the duration of treatment with Tysabri, the level of anti-JCV antibodies in your blood and whether you have received prior treatment with an immunosuppressant medication. Your doctor will discuss the potential risk before you start treatment.

TYSABRI Treatment Continuation Form
TYSABRI (Natalizumab) 300 mg concentrate solution for infusion

This form should be read carefully before continuing TYSABRI treatment for more than 2 years. Although you have been receiving TYSABRI for 2 years, it is important that you are reminded that the risk of PML increases beyond this time. Please follow the advice in this form to ensure that you are fully informed of, and understand the risk of PML (progressive multifocal leukoencephalopathy), IRIS (Immune reconstitution Inflammatory Disease) and other important adverse effects of TYSABRI.

Before continuing treatment with TYSABRI you should:

- **read the Package Leaflet which is included in each box of TYSABRI;**
- **read the Alert Card given to you by your doctor;**
- **discuss with your doctor the benefits and the risks associated this treatment.**

The Package Leaflet and the Alert Card contain important safety information about PML, a rare brain infection that has occurred in patients who have been given TYSABRI and which may lead to severe disability or death.

PML is associated with an uncontrolled increase of the JC virus in the brain, although the reason for this increase in some patients treated with TYSABRI is unknown. JC virus is a common virus which infects many people but does not normally cause noticeable illness.

The risk of PML with TYSABRI is higher

- If you have antibodies to the JC virus in your blood.
- **The longer that you are on treatment with TYSABRI, especially if you have been on treatment for more than two years.**
- If you have taken an immunosuppressant (a medicine that reduces the activity of your body's immune system) at any time before starting TYSABRI treatment.

Your doctor should discuss the potential risk of developing PML with you before you continue treatment with TYSABRI. .

Your doctor may test your blood to check if you have antibodies to the JC virus before you continue treatment with TYSABRI. Your doctor may repeat the test while you are on TYSABRI treatment to check if anything has changed. The risk of PML is higher if you have all the risk factors described above, or if you have not taken an immunosuppressant medication prior to starting TYSABRI and have higher levels of antibodies to the JC virus and you have been on TYSABRI for more than 2 years. Your doctor will monitor you more closely if you are at higher risk for PML

You should discuss with your Doctor if TYSABRI is the most suitable treatment for you before you continue TYSABRI for more than two years.

In patients with PML, a reaction known as IRIS (Immune Reconstitution Inflammatory Syndrome) is likely to occur after treatment for PML, as TYSABRI is removed from your body. IRIS may lead to your condition getting worse, including worsening of brain function.

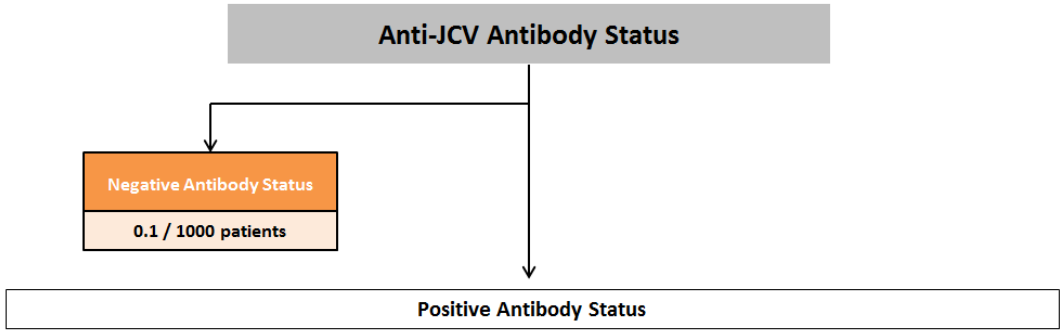
The Package Leaflet should be read each time that you take TYSABRI because it may have new information that is important to your treatment.

You should keep the Alert Card with you to remind you of the important safety information, in particular any symptoms you may develop which could possibly indicate PML, if appropriate, you should show the Alert Card to your partner or caregiver.

If you do not have the Package Leaflet or the Alert Card then please ask your doctor to provide them to you before you receive your infusion of TYSABRI.

[*Patient's name, signature and date of signature, and Doctor's name, signature and date of signature*].

PML risk estimate:



Natalizumab Exposure	PML risk estimates per 1000 patients				
	Patients without prior IS use				Patients with prior IS use
	No index value	Antibody Index ≤ 0.9	Antibody Index > 0.9 ≤ 1.5	Antibody Index > 1.5	
1-12 months	0.1	0.1	0.1	0.2	0.3
13-24 months	0.6	0.1	0.3	0.9	0.4
25-36 months	2	0.2	0.8	3	4
37-48 months	4	0.4	2	7	8
49-60 months	5	0.5	2	8	8
61-72 months	6	0.6	3	10	6

Patients who are anti-JCV antibody negative

Based on global data, if you do not have antibodies to JCV your chance of getting PML is 0.1/1000 (or 1 in 10,000) patients.

Patients who are anti-JCV antibody positive

If you do have antibodies to JCV, your risk of developing PML will vary depending on the duration of treatment with TYSABRI, the level of anti-JCV antibodies in your blood and whether you have received prior treatment with an immunosuppressant medication. Your doctor will discuss the potential risk before you continue with treatment.

TYSABRI Treatment Discontinuation Form
TYSABRI (Natalizumab) 300 mg concentrate solution for infusion

This form should be read carefully at the time of discontinuing treatment with TYSABRI. Please follow the advice in this form to ensure that you are fully informed of, and understand the continued risk of PML (progressive multifocal leukoencephalopathy) for up to 6 months following discontinuation of TYSABRI.

Before starting treatment with TYSABRI you should have received an Alert Card from your doctor. This alert card should be kept for 6 months after discontinuation of treatment as it has important information about PML for your reference.

PML is a rare brain infection that has occurred in patients who have been given TYSABRI and which may lead to severe disability or death. PML has been reported up to 6 months after discontinuation of TYSABRI.

Signs include:

- changes in mental ability and concentration,
- behavioural changes,
- weakness on one side of the body,
- vision problems,
- new neurological symptoms that are unusual for you.

Symptoms of PML may be similar to an MS relapse. Therefore, if you believe your MS is getting worse or if you notice any new symptoms for up to 6 months after stopping TYSABRI treatment, it is very important that you speak to your doctor as soon as possible

During the 6 months following treatment discontinuation of TYSABRI, your doctor will monitor you and will decide when you should receive MRI imaging. In general, you will continue to receive 3-6 month MRI imaging if you have either of the following combination of PML risk factors:

- You have antibodies to the JC virus, have taken TYSABRI for more than 2 years and previously taken an immunosuppressant (a medicine that reduces the activity of your body's immune system) at any time before starting TYSABRI
- You have never taken an immunosuppressant therapy before starting TYSABRI, but have taken TYSABRI for more than 2 years and have a high anti-JCV antibody index (increased amount of antibody in your blood)

If you do not fall into one of the above groups, then you will continue to receive routine MRIs as prescribed by your doctor.

Should you have any questions about the above information, please ask your doctor.

If you do not have the Alert Card that you received when starting TYSABRI, then please ask your doctor for a new card. You should keep the Alert Card with you to remind you of the important safety information, in particular any symptoms you may develop which could possibly indicate PML, if appropriate, you should show the Alert Card to your partner or caregiver.

[*Patient's name, signature and date of signature, and Doctor's name, signature and date of signature*].