Physician* Information and Management Guidelines for Multiple Sclerosis patients on TYSABRI Therapy

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***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 MRI**

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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 I) and is supported by the Treatment Initiation, Continuation and Discontinuation Forms (Appendix 4).

The physician pack also includes a copy of the Patient Information Leaflet (PIL) and Patient Alert Card (Appendices 2 and 3).

It is recommended that physicians initiating and supervising treatment with TYSABRI should share relevant sections of this document with radiologists involved in the differential diagnosis of 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 Progressive Multifocal Leukoencephalopathy (PML)

Prescribers should be aware of the possibility that PML and other opportunistic infections may occur during TYSABRI therapy and should include them 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, their partners and care givers also need to be advised of symptoms that may be indicative of early PML and continue to be vigilant for approximately 6 months following discontinuation (see Section 8.2,Appendix 3: Alert Card and Appendix 4: Treatment Initiation, Continuation and Discontinuation Forms).

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 causes only mild or self-limited disease in people with normally functioning immune systems, but causes more significant disease in people with impaired immunity. Examples include PML, oesophageal candidiasis, systemic fungal infections, *Pneumocystis jiroveci* pneumonia, mycobacterial infections (including atypical mycobacteria, and tuberculosis), chronic intestinal cryptosporidiosis, disseminated viral infections (such as disseminated herpes or cytomegalovirus infections), toxoplasmosis, cryptosporidium infections.

2.2 *Infections Including Opportunistic Infections Associated with TYSABRI*

A case of *Cryptosporidium* diarrhoea was reported in MS clinical trials. In clinical trials in Crohn's Disease, cases of additional opportunistic infections have been reported, some of which were fatal. In these studies concomitant use of other agents including immunosuppressants was common. Occasional reports of other opportunistic infections have been reported with marketed use of TYSABRI.

2.3 *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 post-marketing experience, serious, life-threatening, and sometimes fatal cases have been reported in multiple sclerosis patients receiving TYSABRI.
- Acute retinal necrosis: 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 herpes infections (e.g. herpes meningitis and encephalitis). Patients presenting with eye symptoms such as decreased visual acuity, redness and painful eye should be referred for retinal screening for ARN.

2.4 *Management of Potential Opportunistic Infections*

All TYSABRI treated patients presenting with symptoms of infections should be fully investigated. Early referral to a specialised physician with experience in investigating and managing opportunistic infections should be considered.

In cases of serious infections all efforts must be made to determine the causative organism. If an opportunistic infection is suspected then TYSABRI treatment must be stopped.

2.5 *Progressive Multifocal Leukoencephalopathy (PML)*

2.5.1 Epidemiology

Progressive Multifocal Leukoencephalopathy (PML) is a sub-acute, evolving infectious disease of the Central Nervous System (CNS) caused by the JC 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 treatment of patients with autoimmune disorders and solid organ transplant recipients.

The incidence of PML increased as a consequence of the HIV pandemic. Its prevalence in patients with AIDS was reported as 5%. The introduction of Highly Active Anti Retroviral Therapy (HAART), whilst not reducing the incidence of PML in HIV patients, has been associated with a reduction in mortality (Koralnik, 2004).

An analysis of the 2-step anti-JCV antibody assay (STRATIFY JCV) in over 6,000 MS patients has demonstrated the prevalence of anti-JCV antibodies to be approximately 55%. Anti-JCV antibody prevalence in the EU was reported as ranging from 48.8% to 69.5% in the EU in a cross sectional study of MS patients irrespective of treatment (Bozic *et al.*. 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 using similar methodologies (Egli 2009; Kean 2009; Knowles 2003). In general, anti-JCV antibody prevalence did not appear to be affected by prior immunosuppressant use, prior exposure to TYSABRI, or duration of TYSABRI exposure.

2.5.2 Aetiology

The disease affects the sub-cortical, white matter (Safak and Khalili, 2003) and is caused by the reactivation of JC virus, a human polyomavirus (Berger *et al*., 1998). The triggers for JCV replication are unknown but may result from confluence of risk factors, one of which is a compromised cellular immune system. This can be the consequence of HIV infection, systemic immunosuppression or the use of anti-neoplastic agents, as well as some malignancies.

2.5.3 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 sub-cortical white matter which enlarge and may coalesce with a characteristic pattern on MRI examination.

The presenting 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 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.

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 natalizumab (Agnihotri, 2014; Schippling, 2013). 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 treatment should be suspended if JCV GCN and/or PML is suspected and permanently discontinued if JCV GCN and/or PML is confirmed.

2.5.4 Diagnosis

The EFNS published guidelines for the diagnosis and management of neurological complications of HIV infection including PML (Portegies, 2004). The diagnostic criteria are reproduced here.

Slowly progressive focal neurological deficits with asymmetrical white matter abnormalities on MRI suggest PML. The lesions are generally subcortical in location with finger like projections toward the cortex, and have no mass effect. The lesions are hypointense on T1W MRI sequences, hyperintense on T2W and FLAIR (fluid-attenutated inversion recovery), hyperintense on DWI (diffusion weighted imaging) and generally do not enhance with contrast.

Detection of JCV DNA in the CSF by PCR strongly supports the diagnosis because it has a sensitivity of 72–100% and a specificity of 92–100% (Cinque *et al.*, 1997). If the CSF-PCR is negative, it is recommended to repeat CSF-PCR. Use of an ultrasensitive PCR JCV DNA test is important (e.g., with a Limit of Detection (LoD) of 10 copies/mL) as many confirmed PML cases have demonstrated a low copy count. Brain biopsy remains the final confirmatory test, but a positive CSF-PCR offers acceptable evidence. MRI is the sensitive paraclinical tool for detection of symptomatic and asymptomatic PML in TYSABRI treated patients (Wattjes and Barkhof, 2014). A previous baseline brain MRI scan should be available for use as a reference to help in differentiating between PML and other neurological diseases, e.g., MS lesions.

A detailed diagnostic algorithm has been developed to assist physicians with the assessment of new or worsening neurological symptoms in TYSABRI treated MS patients. This is described in detail in Section 3 of this guidance document.

2.6 *PML in TYSABRI Treated Patients*

During extended pre-registration trials, two cases of PML were reported in MS patients and a full safety evaluation revealed one further case in a clinical trial patient with Crohn's Disease (Yousry, 2006). In the post-marketing setting, the risk of PML has been well characterized over the first 6 years of treatment with the identification of different levels of PML risk in different patient subgroups (see below).

2.7 *PML Risk Factors*

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

- **The presence of anti-JCV antibodies.** Patients who are anti-JCV antibody positive are at an increased risk of developing PML compared to 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 treatment duration, especially beyond 2 years.
- **Prior immunosuppressant (IS) treatment**. Patients who have a history of treatment with an immunosuppressant prior to starting TYSABRI are also at increased risk of developing PML

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 higher risk of PML. In anti-JCV antibody positive TYSABRI treated patients who have not used prior immunosuppressants the level of anti-JCV antibody response (index) is associated with the level of risk for PML (i.e. the risk is greater in those with a high antibody index compared to those with a low index). Currently available evidence suggests that the risk of PML is low at an index equal to or below 0.9 and increases substantially above 1.5 for patients who have been on treatment with TYSABRI for longer than 2 years.

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 following discontinuation of therapy.

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

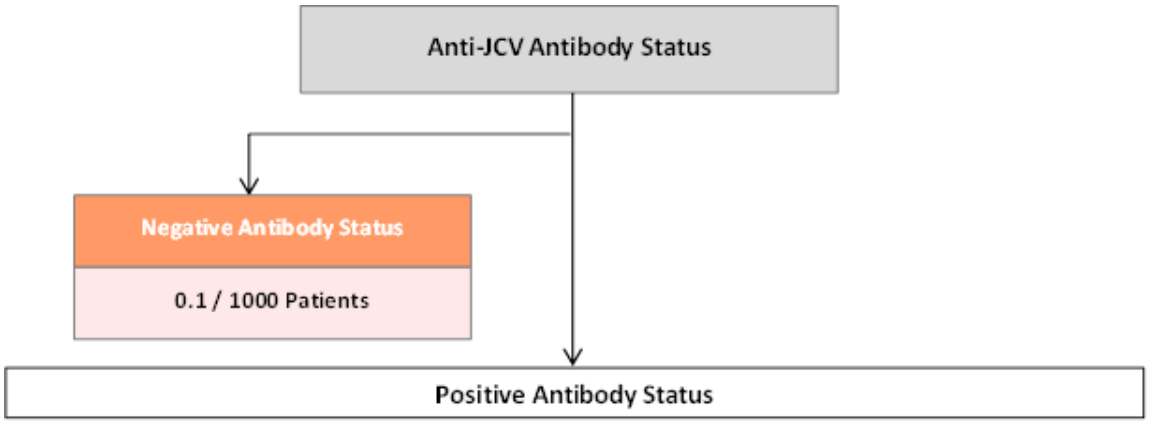
- For anti-JCV antibody negative patients: PML risk estimates are based on post-marketing data from approximately 125,000 TYSABRI exposed patients where the estimated incidence of PML for anti-JCV antibody negative patients is 0.1/1000. Anti-JCV antibody negative patients may still be at risk of PML 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 Life Table Method based on the pooled cohort of 21,696 patients who participated in the STRATIFY-2, TOP, TYGRIS, and STRATA clinical studies. The risk estimates from the Life Table Method are forward-looking in yearly intervals (for example the risk estimate corresponding to the 25-36 month natalizumab 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 (eg, treatment discontinuation) accounted for.

- For anti-JCV antibody positive patients who have not used prior immunosuppressants: 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, since prior IS use is recognized 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 does 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

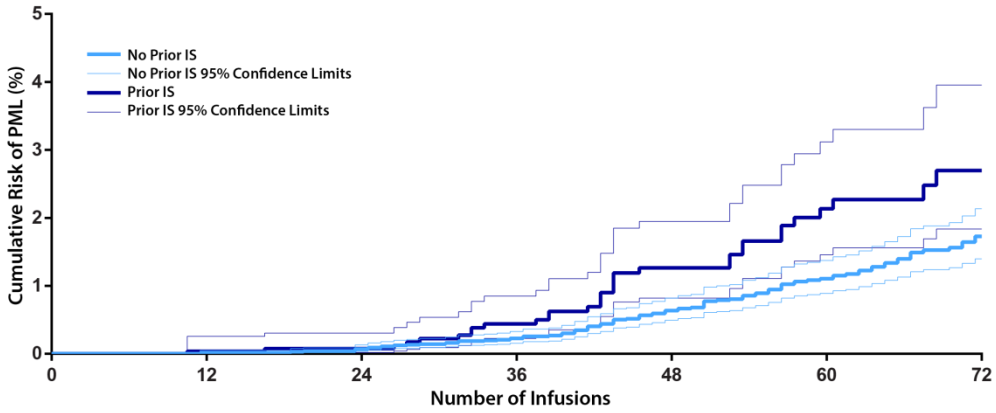


Natalizumab Exposure	PML risk estimates per 1000 patients				
	Patients without prior IS use				Patients with Prior IS use
	No index value	Antibody Index ≤ 0.9	Antibody Index > 0.9 ≤ 1.5	Antibody Index > 1.5	
1-12 months	0.1	0.1	0.1	0.2	0.3
13-24 months	0.6	0.1	0.3	0.9	0.4
25-36 months	2	0.2	0.8	3	4
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

PML risk estimates in anti-JCV antibody positive patients were derived using Life Table Method based on the pooled cohort of 21,696 patients who participated in the STRATIFY-2, TOP, TYGRIS, and STRATA clinical studies. Further stratification of PML risk by anti-JCV antibody index interval for patients with no prior use of immunosuppressant 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 were estimated based on post-marketing data from approximately 125,000 TYSABRI exposed patients.

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 time point represent the total cumulative risk up to that time point (for example, at the time point 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 takes 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



	Number of Subjects at Risk (a)						
No Prior IS	18,616	16,130	12,925	9,755	6,880	4,379	2,277
Prior IS	3,080	2,671	2,201	1,693	1,159	720	366
	Cumulative Number of PML Cases (b)						
No Prior IS	0	2	10	28	62	89	109
Prior IS	0	1	2	9	21	29	32

NOTE 1: Number of PML cases after 72 infusions: No Prior IS = 11, Prior IS = 4. NOTE 2: For patients with missing data on anti-JCV antibody status and/or prior IS use, multiple imputation methodology us 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

2.8 *Recommended Patient monitoring*

Testing for Anti-JCV Antibodies

Serum 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 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. Re-testing of anti-JCV antibody negative patients every 6 months is recommended. Re-testing low index patients who have no history of prior immunosuppressant use every 6 months once they reach the 2 year treatment point is recommended to inform on appropriate patient MRI monitoring.

In the STRATIFY-1 clinical study approximately 11% of patients changed serostatus from anti-JCV antibody negative to positive per year. Approximately 12-16% serostatus change from antibody negative to positive in the second generation assay was reported in Unilabs real world data over a median duration of 12 months. In the STRATIFY-2 clinical study approximately 6% of patients changed serostatus from anti-JCV antibody positive to negative per year. Patients who test anti-JCV antibody positive at any time should be considered to be at an increased risk for developing PML, independent from any prior or subsequent antibody test results. From available longitudinal STRATIFY-2 study, in patients who changed serostatus from positive to negative, the median last index level before testing antibody negative was 0.44 (25th quartile = 0.34; 75th quartile = 0.55), which was close to the cut-off index level of 0.4). Furthermore, findings from another longitudinal study showed that 1 in 13 seropositive patients seroreverted to negative, mostly in patients with a titre of ≤0.6, i.e. also close to the cut-off point for positive/negative.

Patients who test anti-JCV antibody positive at any time should be considered to be at an increased risk for developing PML, independent from any prior or subsequent antibody test results.

Testing should only be performed using an appropriate and validated assay e.g. STRATIFY JCV. 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 two weeks following, plasma exchange due to the removal of antibodies from the serum.

Recommended MRI monitoring

MRI in the clinical practice of MS has been shown to be a useful tool for patient monitoring. It may assist in differentiating PML lesions from MS plaques in patients that develop new neurological symptoms or signs once on therapy. Recommendations for MRI monitoring is summarized below:

a) **Recent MRI (usually within 3 months) prior to initiation of TYSABRI is recommended. MRI should be performed at least on a yearly basis.** Clinicians should evaluate the yearly MRI in asymptomatic patients on TYSABRI for any signs of PML.

b) **More frequent MRI monitoring every 3-6 months using an abbreviated protocol should be considered in patients at a 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

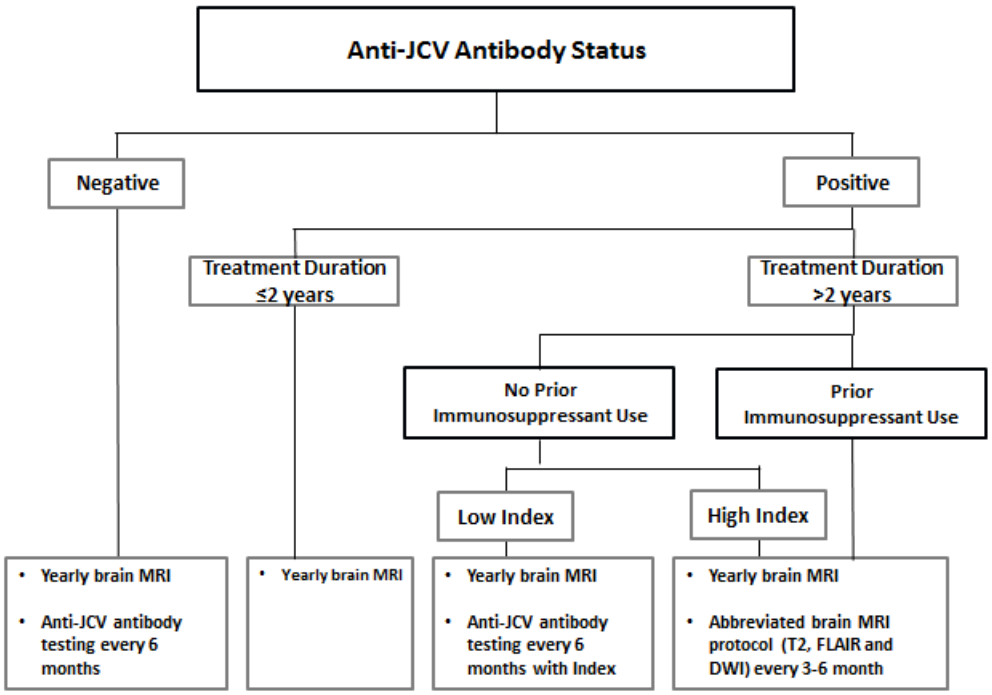
- Patients with a high anti-JCV antibody index who have received more than 2 years of TYSABRI therapy and without prior history of immunosuppressant therapy.

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 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.

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 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 above).

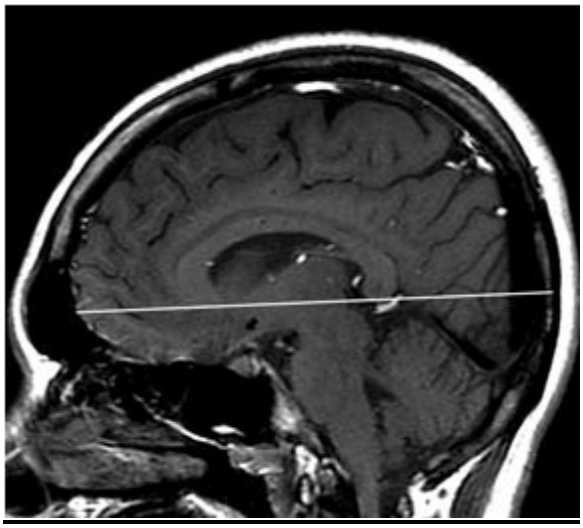
A summary of the recommended monitoring is provided in Figure 3.

Figure 3: Recommended Patient Monitoring



Standard brain MRI protocol (for baseline and routine annual scans for all patients):

- ***Scanner field strength >1.0 T, slice thickness <5 mm with no gap and with whole brain coverage***
- ***Axial images prescribed from the subcallosal line***



Full MRI Protocol
Sagittal and axial 2D FLAIR or 3D FLAIR
Axial FSE PD/T2
Axial DWI
Axial T1W spin echo pre and post contrast
Gd injection 0.1 mmol/kg over 30 seconds
5-minute delay after contrast injection

More frequent MRIs in higher risk patients should be performed using an abbreviated protocol. (FLAIR/T2-weighted and diffusion weighted imaging [DWI]).

Abbreviated MRI protocol (screening MRI) for safety monitoring in high risk patients
Sagittal and axial 2D FLAIR
Axial FSE PD/T2W
Axial DWI

If MRI lesions are suggestive of PML, a full MRI protocol with contrast enhancement should be performed.

When MRI lesions suggestive for PML are detected, the MRI protocol should be extended to include contrast-enhanced T1-weighted imaging to detect inflammatory features and the possible coincidence of PML and PML-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.

3 Diagnosis of PML

Including clinical and MRI differentiation between PML and MS symptoms/lesions.

3.1 *General Principles*

The following points should be considered when undertaking the clinical management of MS patients on TYSABRI therapy.

- 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, their partners and care givers need to be advised of symptoms that may be indicative of early PML (see Section 8.2,Appendix 3: Alert Cardand Appendix 4: Treatment Initiation,Continuation and Discontinuation Forms) and be counseled on the need to be vigilant for these symptoms while on TYSABRI treatment, and also for approximately 6 months after the last dose of TYSABRI (PML has also been reported up to 6 months following 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 short duration (days or weeks), is not expected to compromise therapeutic efficacy based on the pharmacodynamics of the drug.**

- The decision to suspend TYSABRI at any stage 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.**

- **TYSABRI dosing should only be restarted when the diagnosis of PML is excluded (if necessary, by repeating clinical, MRI and laboratory investigations if suspicion of PML remains).**

3.2 *Clinical Differentiation between PML and MS Relapse*

The following guidance and algorithm (Figure 4) describes a suggested approach to the clinical assessment of new or worsening neurological symptoms in MS patients treated with TYSABRI.

New or recurrent neurological symptoms should prompt careful evaluation in order to assess the underlying pathology e.g. MS or PML. It is important to note that presence of new onset neurologic symptoms are not required to diagnose PML in the setting of MRI findings consistent with PML and the presence of JC virus in the central nervous system (CSF or in brain tissue). Cases of asymptomatic PML have been reported. In both high and low risk asymptomatic patients, any new suspected lesion at

recommended MRI evaluation for monitoring PML risk should be carefully evaluated, particularly when an abbreviated protocol has been performed (see following section MRI Differentiation between PML and MS relapse). Table 1 highlights the clinical features that help differentiate MS from PML. It should be noted that the table is not all inclusive and there may be a great deal of overlap between symptoms of the two conditions. Physicians should be aware that the clinical picture 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.

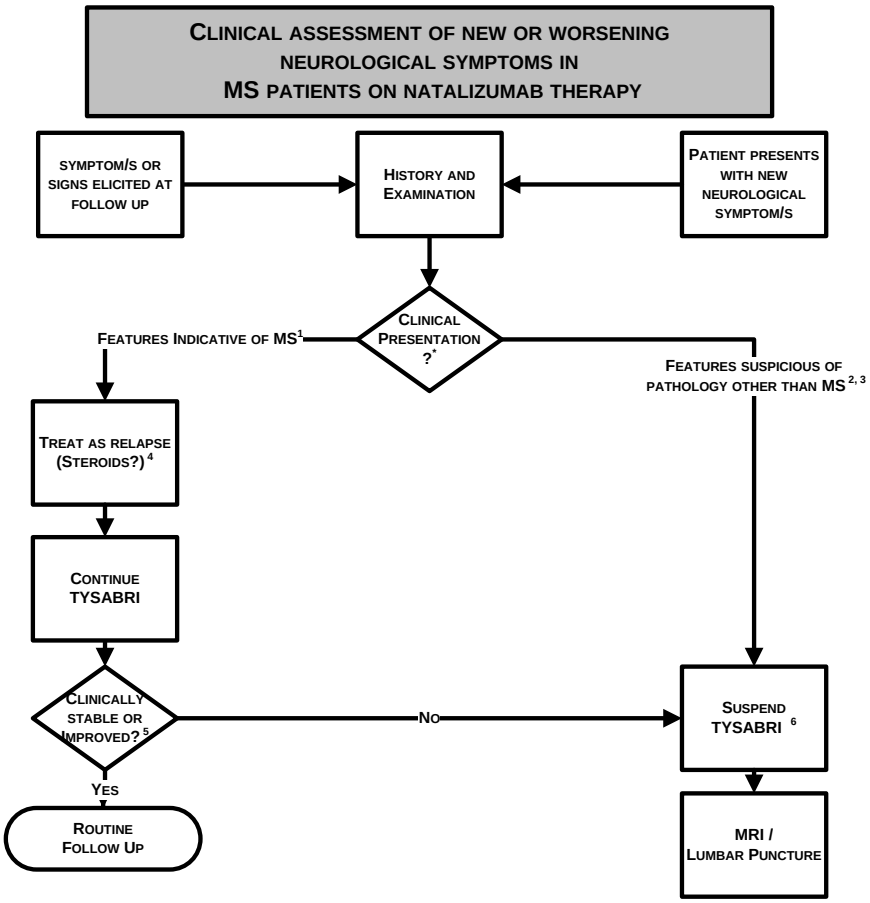
Table 1. Clinical Features of MS and PML

	Features Indicative of :	
	MS [1]	**PML[2]**
Onset	Acute	Sub-acute
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)

Reference: Kappos *et al*., 2011

If the clinical presentation cannot exclude PML, further investigations including MRI evaluation (Figure 5, Table 2) and / or lumbar puncture and cerebrospinal fluid (CSF) evaluation (Figure 6) should be undertaken as soon as possible. A definitive diagnosis of PML should only be made on the basis of a clinical presentation or MRI findings and the identification of JC viral DNA in the central nervous system (CNS).

Figure 4. Clinical Assessment



[1] See Table 1

[2] See Table 1

[3] Clinicians should consider other non-MS pathology in addition to PML especially opportunistic infections

[4] Relapses should be managed according to usual clinical practice. A single, short course of steroids can be considered in cases where PML is unlikely on clinical grounds. Lack of response to steroids should be a trigger for further investigation.

[5] Clinical findings should be compared with those recorded at clinical presentation* of this episode

[6] If non MS pathology is suspected at clinical presentation or during follow up **ALL future infusions** should be postponed until PML or other opportunistic infections have been definitively excluded

Reference: Kappos *et al.*, 2011

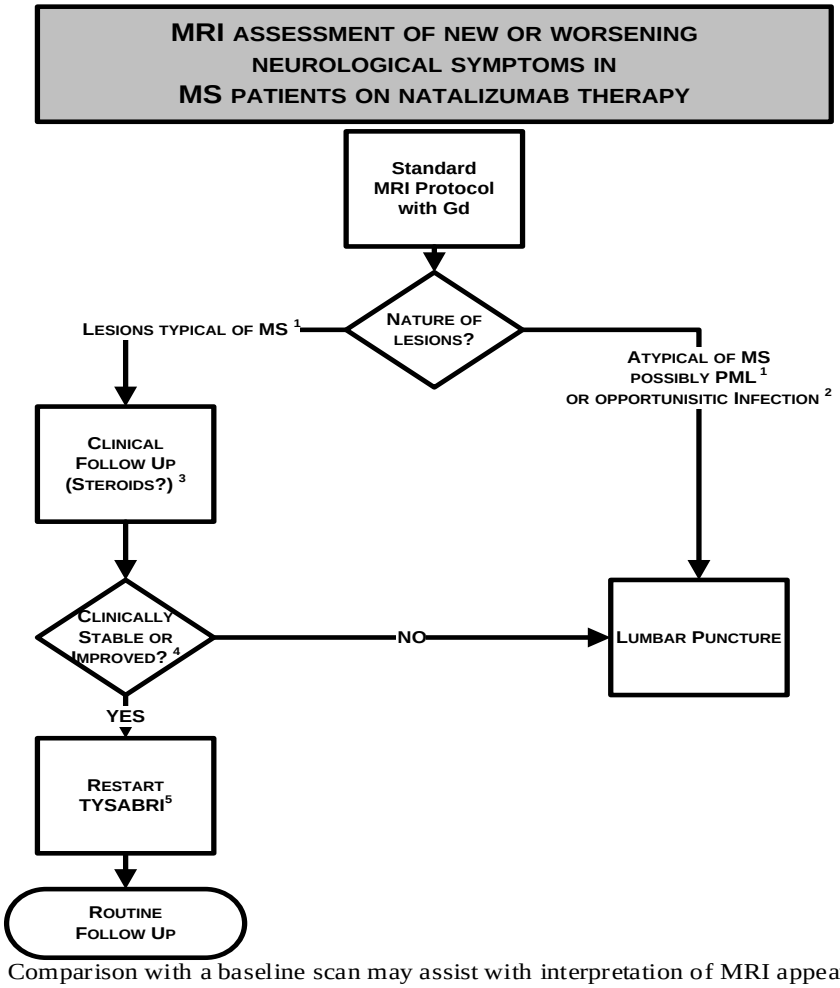
3.3 *MRI Differentiation between PML and MS Relapse*

A standardized MRI protocol preferably with and without contrast for the follow-up of patients on TYSABRI is proposed to obtain the best possible images for clinical decision making to assist with clinical decision-making (Yousry *et al*., 2006, Yousry 2012). FLAIR is the most sensitive sequence for detection of PML (Wattjes *et al.*. Nat. Rev. Neurol. 2015). Diffusion-weighted imaging sequences may also be helpful in distinguishing new lesions from chronic MS plaques and MRI changes from a previous scan (Wattjes *et al.*, 2015; Mader *et al.*, 2003). 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 recognition of early alterations on MRI (Table 2).

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

Figure 5. MRI Assessment (See Section 3.1) TYSABRI must be suspended and not restarted until non MS pathology has been confidently excluded.

If PML is suspected based on a clinical presentation and an MRI is not readily available, laboratory investigations e.g. lumbar puncture to exclude PML should not be delayed.



[1] See Table 2 Comparison with a baseline scan may assist with interpretation of MRI appearances

[2] Clinicians should consider other non-MS pathology in addition to PML especially opportunistic infections

[3] Relapses should be managed according to usual clinical practice. A single, short course of steroids can be considered in cases where PML is unlikely on clinical grounds. Lack of response to steroids should be a trigger for further investigation.

[4] Clinical findings should be compared with those recorded at clinical presentation of this episode

[5] Resumption of TYSABRI therapy must only be considered once **PML or other opportunistic infections have been definitively excluded** on the basis of clinical findings and/or further investigations.

Reference: Kappos et al, 2011

Table 2. Features Visualised on MRI
To be considered in the differential diagnosis of MS and PML.

Feature	Multiple Sclerosis	PML
Lesion location	Focal, periventricular or deep white matter. Lesions occur in all areas of the brain , optic nerves and spinal cord.	Asymetetric , focal or multifocal . Subcortical or diffuse white matter. cortical grey matter, and deep gray 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 edema	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 edema	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 WM disease. No restriction on ADC
Atrophy	Diffuse atrophy with progressive MS disease	Post PML-IRIS –encephalomalacia and diffuse brain atrophy in the affected areas.

(Reference: Kappos 2011; Yousry 2012, Wattjes & Barkhof 2014)

Laboratory Differentiation of PML from MS Relapse

This algorithm suggests how laboratory investigations can be integrated with clinical and MRI assessments in patients treated with TYSABRI (Figure 6).

The detection of JCV DNA by PCR in the cerebrospinal fluid 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. Depending on the clinical presentation and the availability of MRI resources the analysis of CSF may well be conducted early. If JCV DNA is not detected in CSF and if clinical and/or suspicion of PML remains high, a repeat lumbar puncture should be performed. 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 the recommended 10 copies/mL (see below), and clinical and MRI suspicion remains high.

CSF analysis for JCV DNA

CSF samples should be analysed as quickly as possible to facilitate the diagnosis of PML.

Assays should be based on quantitative real time PCR methodology to maximize sensitivity and specificity for detection and it is recommended to use an assay with a Limit of Detection (LoD) of at least 10 copies/mL. This level of detection is diagnostically relevant since PML has been confirmed in patients with low copy numbers in the CSF.

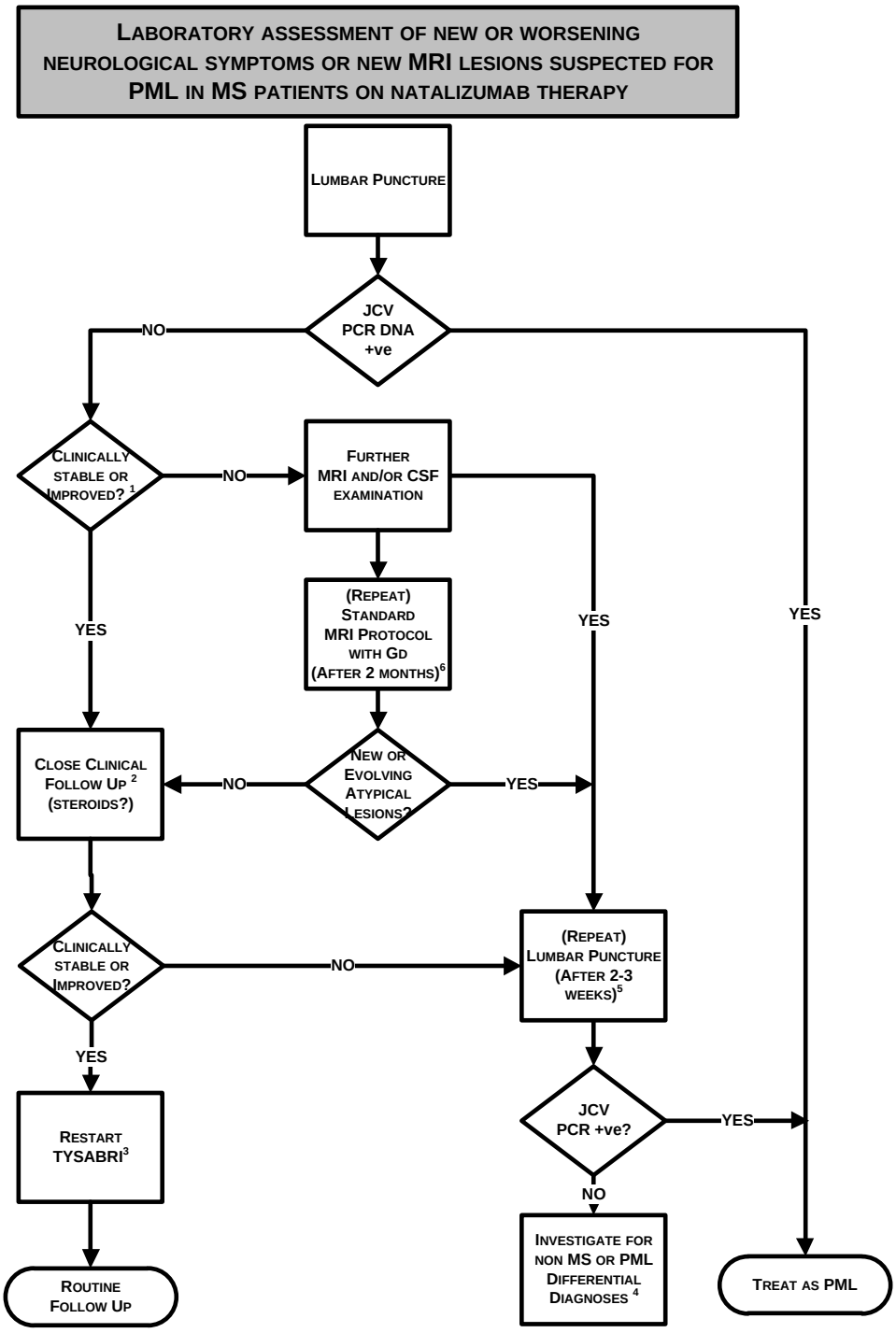
If continued clinical or MRI-based suspicion of PML persists despite a local or reference laboratory result being negative (i.e. not detected) for JCV DNA by PCR, and especially if the result is based on an assay with a LoD that is less sensitive than the recommended 10 copies/mL, a further test for JCV DNA (the same CSF sample or a fresh aliquot) is recommended.

The Marketing Authorisation Holder (MAH) is not in a position to certify any laboratory. However, the MAH is aware of two central laboratories (Focus Diagnostics, Cypress, California and Unilabs, Copenhagen, Denmark) that offer a real time PCR assay specific for detection of JCV DNA in the cerebrospinal fluid.

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 a LoD of 10 copies/ml. A head-to-head comparison of the sensitivity of the assays performed at Unilabs and NIH (National Institute of Health in the USA) has not been carried out. However, the two sensitivity assessments have been described as similar in the literature published by the NIH as similar viral standards and controls have been used in development of the assay.

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

Figure 6. Laboratory Differentiation (See Section 3.1, TYSABRI must be suspended and not restarted until non MS pathology has been confidently excluded).



[1] Clinical findings should be compared with those recorded at clinical presentation of this episode

[2] Close clinical follow would be at least bi-weekly assessments.Relapses should be managed according to usual clinical practice. A single, short course of steroids can be considered in cases where PML is unlikely on clinical grounds. Lack of response to steroids should be a trigger for further investigation.

[3] Resumption of TYSABRI therapy must only be considered once PML or other opportunistic infection has been excluded on the basis of clinical findings and/or further investigations.

[4] Clinicians should consider other non-MS pathology in addition to PML especially opportunistic infections, or consider brain biopsy to confirm/discount presence of JCV

[5] Accelerate retesting if aggressive clinical symptoms persist.

[6] Or earlier if required.

4 Management of PML

Overall, the use of antiviral agents, such as cidofovir and cytarabine, to treat PML has proven ineffective in improving the outcome in patients with PML (Hall 1998; Aksamit 2001; Marra 2002; Gasnault 2001).

Immune reconstitution (restoration of normal immune function) appears to be the most effective treatment with evidence stemming from two areas of study. The first is in HIV where if PML occurs in an untreated patient, introduction of HAART can reverse the disease and improve outcome. Secondly, when PML occurs in transplant patients, if immune suppression can be reduced, outcome may be improved.

The data available suggests that early PML recognition and intervention may improve outcome (Antinori *et al.*, 2003; Berenguer *et al.*, 2003; Clifford *et al.*, 1999; Crowder *et al.*, 2005; Geschwind *et al.*, 2001; Shitrit *et al.*, 2005). It is possible that the earlier recognition of PML and discontinuation of TYSABRI allows immune reconstitution which contributed to the survival of the MS patient reported by Langer-Gould and colleagues (2005). The effect of plasma exchange (PLEX) on TYSABRI clearance and pharmacodynamics was evaluated in a study of 12 MS patients. An estimate of the total drug removal after 3 plasma exchanges (over a 5-8 day interval) was approximately 70-80% (Khatri *et al.*, 2009). This compares to approximately 40% reduction observed by drug discontinuation alone (without plasma exchange) over a similar period of observation. These data also suggest that additional plasma exchanges (up to a total of 5 over a 10 day period) may be required to more consistently reduce TYSABRI concentrations to below sub-therapeutic levels. This may be helpful to restore immunocompetence more quickly and therefore possibly control the JC virus infection. The clinical usefulness of plasma exchange or immunoadsorption to remove TYSABRI and accelerate immune reconstitution is unknown. A review of further cases together with an assessment of the long-term clinical status of patients post-PLEX or immunoadsorption is required before any robust conclusions can be made on clinical usefulness of this intervention. In addition, physicians do need to be aware of one consequence of immune reconstitution to assist with recovery from PML. IRIS (see below) with clinical associated deterioration may occur before improvement is seen. This clinical condition has been observed in the majority of post-marketing PML cases to date.

4.1 *Immune Reconstitution Inflammatory Syndrome (IRIS)*

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 immune reconstitution inflammatory syndrome (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 local inflammatory reaction, including oedema, and manifests as a worsening of neurological symptoms including hemiparesis, ataxia, speech abnormalities, visual disturbance, cognitive/behavioural changes and seizure (dependent on the site of IRIS). Severe sequelae can occur including coma and death. Although JC viral 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 (BBB) and release of JCV from cells lysed during IRIS, it can be increased.

In HIV patients, IRIS usually occurs within 2 to 3 months of initiation of HAART. In patients treated with TYSABRI, IRIS has occurred within days to several weeks after TYSABRI removal by plasma exchange (PLEX) or immunoabsorption (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 (Talan 2009; Elston and Thacker 2009) and 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 (Tan *et al.,* 2009, Clifford *et al.,* 2010). 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 wks with taper over 2 months

2) Intravenous methylprednisolone (1 g/d for 3 or 5 d) with oral taper over 2 months

If further deterioration occurs during 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. 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.

5 Prognosis

Early diagnosis, clinical and MRI monitoring, stopping TYSABRI therapy, and the use of plasma exchange (PLEX) may have improved the outcome of PML in affected TYSABRI patients.

Of the 582 confirmed postmarketing PML cases reported globally as of 07 August 2015, 173 cases were from clinical or observational studies, and 409 cases were reported spontaneously. The survival rate for confirmed postmarketing patients with PML is 77% (448 of 582 patients are alive), and the mortality rate is 23% (134 of 582 patients died).

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. As of 04 June 2015, 62 of 566 confirmed PML cases (10.9%) were clinically asymptomatic at the time of PML diagnosis and were initially identified by MRI. Follow-up was available for 48 of the 62 cases (77.4%) with a mean and median duration of follow-up of 12.4 and 11.8 months (range 1 to 33.6 months). At the time of last follow-up, 95% (59/62) of patients were alive and three had a fatal outcome. At the time of the analysis, 63% (39/62) of patients with asymptomatic onset had at least 6 months of follow-up data available. Of the 48 patients for whom follow-up information was available, the majority (70.8%; 34/48) remained free from clinical symptoms, while 29.1% (14/48) became symptomatic subsequent to PML diagnosis. For the patients who became symptomatic, the median time from first suspect MRI to the onset of symptoms was 17 days (mean 32.2 days, range 1-151).

Asymptomatic PML patients had a shorter time from suspicion of PML to diagnosis of PML compared to symptomatic PML patients (median of 28 days versus 53 days). In addition, asymptomatic PML patients had more localized PML on brain MRI at time of

suspicion compared to symptomatic PML patients. There was a higher proportion of asymptomatic PML patients that had unilobar PML lesions on MRI at the time of diagnosis compared to symptomatic PML patients (60% versus 37%). Conversely, 16% of asymptomatic patients had widespread PML on MRI compared to 40% of symptomatic patients.

Asymptomatic patients appear to have less accrual of disability overtime as reflected by lower EDSS scores and higher Karnofsky scores after PML diagnosis compared to symptomatic patients (symptomatic patients did, however, have a slightly higher level of disability pre-PML compared to asymptomatic patients). Asymptomatic PML patients also had a higher survival rate compared to symptomatic patients (95% versus 74%).

6 PML diagnosed after discontinuation of Natalizumab

While the majority of cases of PML have occurred during treatment with TYSABRI, there have been reports of cases identified more than four weeks after the last infusion. Of the 566 confirmed cases of PML reported as of 4 June 2015 PML onset was known for 98% (555). Seventy-four (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 (88%) were alive at the time of the analysis. TYSABRI exposure ranged from 8 to 90 months (mean 43 and median 42.5), with the majority of the patients (81%; 60/74) 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 and median of 2.1 and 1.8 months, respectively; the majority of cases (88%; 65/74) occurred within 3 months of the last infusion of TYSABRI.

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

7 Adverse Reactions associated with infusions

7.1 *Hypersensitivity*

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. All patients recovered without sequelae.

Hypersensitivity reactions usually occurred during the infusion or within the 1-hour period after the 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 an extended period (three months or more) without treatment. However, the risk of hypersensitivity reactions should be considered for every infusion administered.

7.2 *Managing Infusion Hypersensitivity Reactions in Clinical Practice*

Resources for the management of hypersensitivity reactions should be available.

After dilution, 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. In the case of hypersensitivity during the infusion (e.g. urticaria with or without associated systemic symptoms, anaphylaxis), administration of the drug should be stopped immediately, and vascular access maintained for emergency treatment and fluid support. Immediate hypersensitivity reactions should be treated according to the severity of the reaction and the facility's Standard Operating Procedure. Patients who have experienced a hypersensitivity reaction must be permanently discontinued from treatment with TYSABRI.

7.3 *Other Adverse Reactions Associated with Infusions*

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 TYSABRI (placebo: 18.7%). Infusion reactions also occurred more frequently in patients re-exposed to TYSABRI following an initial short exposure (one or two infusions) and an extended period (three months or more) without treatment. In addition to hypersensitivity reactions reported, events reported more commonly with TYSABRI than with placebo included dizziness, nausea, urticaria and rigors. These events were usually mild in severity, resolved at the end of the infusions and did not require interruption of treatment. If individual symptoms are problematic symptomatic treatment may be helpful but there are no data available concerning this.

7.4 *Anti-Natalizumab Antibodies in Clinical Practice*

After approximately 6 months of therapy, persistent antibodies should be considered if there is either reduced efficacy or persistence of adverse events related to infusions (patients that experience a hypersensitivity reaction should be discontinued). 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 the efficacy of TYSABRI and an increased incidence of hypersensitivity reactions. Patients who have received an initial short exposure to TYSABRI (1-2 infusions) and then had an extended period without treatment are at a higher risk of developing anti-natalizumab antibodies and/or hypersensitivity upon redosing. Therefore, the presence of anti-natalizumab antibodies should be evaluated and if these remain positive in a confirmatory test after at least six weeks, the patient should not receive further treatment with TYSABRI.

Anti natalizumab antibody tests may obtained at:
Florian Deisenhammer MD, MSc
Professor of Neurology
Neuroimmunology Laboratory
Innsbruck Medical University
Innrain 66, 2nd floor
6020 Innsbruck, Austria
Tel: +43 512 504 24264

Fax: +43 512 504 24266

8 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 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 treatment should be individually reconsidered by the specialist physician and the patient. The patient should be re-informed about the risks of PML with TYSABRI after 24 months, and should be instructed together with their caregivers on early signs and symptoms of PML. Patients who are discontinuing TYSABRI treatment should also be informed that cases of PML have occurred in patients up to 6-months after the last does of TYSABRI. In this situation, the same monitoring protocol should be continued for approximately six months following discontinuation of TYSABRI. Template treatment initiation, continuation and discontinuation forms are provided in Appendix 4.

8.1 *Informing Patients about Benefits and Risks*

The Patient Information Leaflet (PIL) 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 parts of this pack (Appendix 2) so that the physician can become familiar with the PIL prior to counseling patients about TYSABRI therapy.

Physicians should counsel patients on the importance of uninterrupted dosing, particularly in the early months of treatment (see Section 7.1, Hypersensitivity).

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 a locally agreed template for a treatment initiation information sheet and a treatment continuation sheet at 24 months of treatment and a discontinuation form describing specifically the risk of PML with TYSABRI treatment and the importance of monitoring for PML are provided in appendix 4. These should be provided to patients before initiation of treatment, after 24 months of treatment, and following discontinuation to ensure that patients are fully informed about the risk of PML.

Call for reporting

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.
Suspected adverse reactions and medication errors should be reported. Report forms can be downloaded from http://www.medicinesauthority.gov.mt/adrportal and sent by post or email to:
P: ADR reporting/Sir Temi Zammit Buildings, Malta Life Sciences Park, San Gwann SGN 3000, Malta
E: postlicensing.medicinesauthority@gov.mt

8.2 *Alert Card*

The Alert Card must be issued to patients.

It reminds patients that because of the risks of PML associated with TYSABRI they must contact their doctor if they believe 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 and communication difficulties. Partners and care givers should also be made aware of the information provided in the Alert Card. The Alert Card, includes a recommendation for patients to retain the card for a period of 6 months following the last dose of TYSABRI treatment since signs and symptoms suggestive of PML may occur up to 6 months after discontinuation and patients and their 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 doctor must complete this section when issuing the card.

Alert Cards 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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10 Appendices

Appendix 1. Summary of Product Characteristics (SmPC)

Appendix 2. Patient Information Leaflet (PIL)

Appendix 3. Patient Alert Card

Appendix 4. Treatment Initiation, Continuation and Discontinuation Forms

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

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 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 via:

Ireland
HPRA Pharmacovigilance
Earlsfort Terrace
IRL - Dublin 2
Tel: +353 1 6764971
Fax: +353 1 6762517
Website: www.hpra.ie
e-mail: medsafety@hpra.ie

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

United Kingdom
Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard

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).

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

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Berkshire,
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United Kingdom

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

02/2017

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

Appendix 2. Patient Information Leaflet (PIL)

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
2. What you need to know before you use TYSABRI
3. How to use TYSABRI
4. Possible side effects
5. How to store TYSABRI
6. Contents of the pack and other information

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
Earlsfort Terrace
IRL - Dublin 2
Tel: +353 1 6764971
Fax: +353 1 6762517
Website: www.hpra.ie
e-mail: medsafety@hpra.ie

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

United Kingdom
Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard

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
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This leaflet was last revised in 02/2017.

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

Appendix 3. Patient Alert Card

TYSABRI▼ Patient Alert Card

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.

- 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 of symptoms that might arise for up to 6 months after stopping TYSABRI treatment.

Prior to treatment with TYSABRI

During 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 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:
- 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.

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

• 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	TYSABRI. Speak to your doctor as soon as possible if you think you have developed a severe, persistent infection, for example a persistent fever. **Reporting of side effects** ▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in the package leaflet. You can also report them directly via the national reporting system at: www.mhra.gov.uk/ yellowcard (UK), or if in Ireland, or if in Ireland, via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6712517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

Appendix 4. Treatment Initiation, Continuation and Discontinuation Forms

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.

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 PML risk diagram (Figure 1) 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. If you do not have antibodies to the JC virus, your doctor should repeat the test regularly to check if anything has changed. The risk of PML is higher in patients who have antibodies to the JC virus compared to patients who do not have antibodies to the JC virus.

If you have all three risks described above your chance of getting PML is approximately 11 in 1000 patients treated. 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.

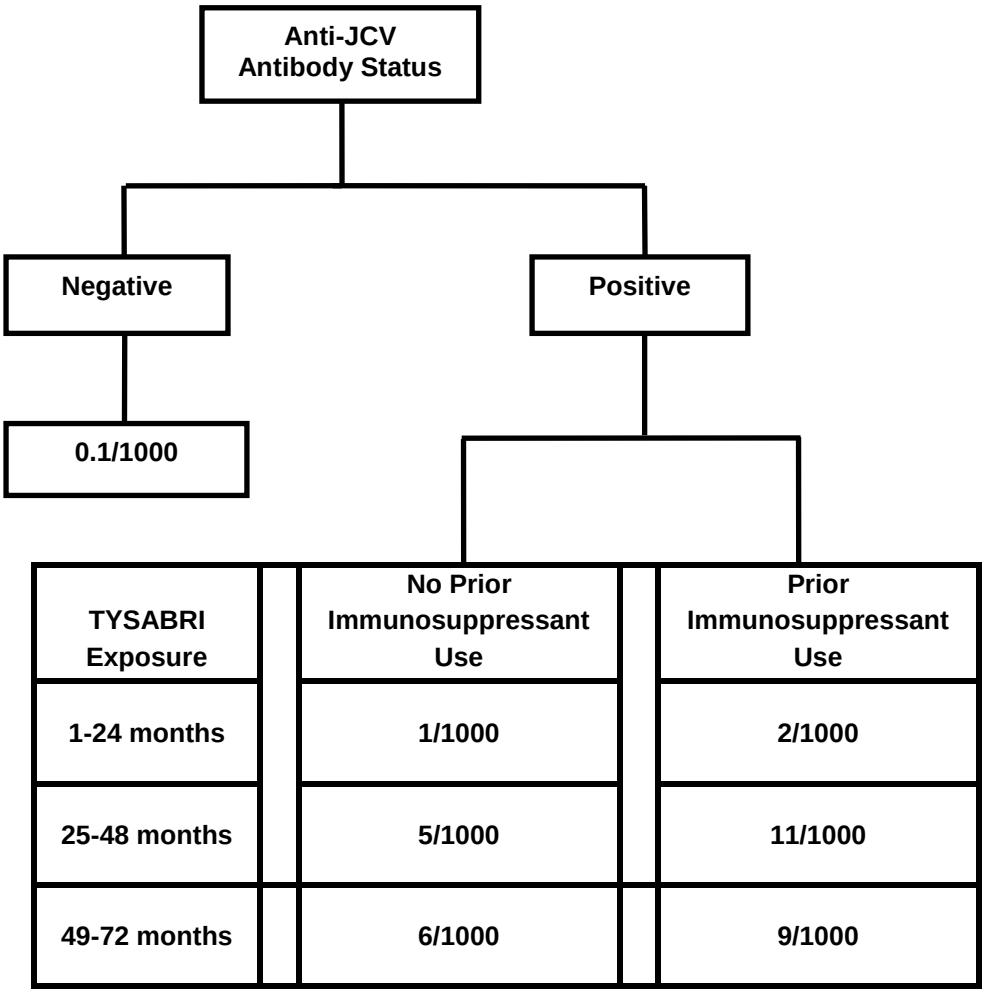
The Package Leaflet should be read each time that you take TYSABRI because it may have new information that is important to your treatment.

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*].

Figure 1. PML Risk Diagram



TYSABRI Exposure	No Prior Immunosuppressant Use	Prior Immunosuppressant Use
1-24 months	1/1000	2/1000
25-48 months	5/1000	11/1000
49-72 months	6/1000	9/1000

Risk diagram updated October 2014

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 PML risk diagram (Figure 1) 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. If you do not have antibodies to the JC virus, your doctor should repeat the test regularly to check if anything has changed. The risk of PML is higher in patients who have antibodies to the JC virus compared to patients who do not have antibodies to the JC virus.

If you have all three risks described above your chance of getting PML is approximately 11 in 1000 patients treated. You should discuss with your Doctor if TYSABRI is the most suitable treatment for you before you continue TYSABRI for more than two years.

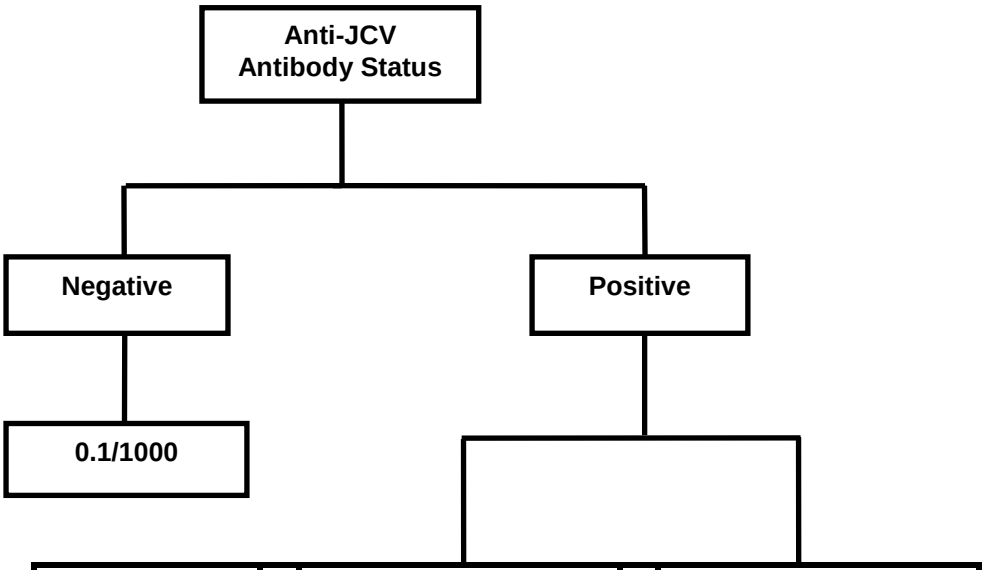
In patients with PML, a reaction known as IRIS (Immune Reconstitution Inflammatory Syndrome) is likely to occur after treatment for PML, as TYSABRI is removed from your body. IRIS may lead to your condition getting worse, including worsening of brain function.

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*



TYSABRI Exposure	No Prior Immunosuppressant Use	Prior Immunosuppressant Use
1-24 months	1/1000	2/1000
25-48 months	5/1000	11/1000
49-72 months	6/1000	9/1000

Risk diagram updated October 2014

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

This form should be read carefully before 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*].

Reporting of side effects

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in the package leaflet. Suspected adverse reactions and medication errors should be reported. Report forms can be downloaded from http://www.medicinesauthority.gov.mt/adrportal and sent by post or email to:

P: ADR reporting/Sir Temi Zammit Buildings, Malta Life Sciences Park, San Gwann SGN 3000, Malta

E: postlicensing.medicinesauthority@gov.mt