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

Version 14: 22 May 2015

***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**

Table of Contents

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 and Continuation 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 5 months after the last dose of Tysabri. Patients, their partners and care givers 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 6.2 and Appendix 3: Alert Card, Appendix 4: Treatment Initiation and Continuation 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*

In clinical trials, herpes infections (Varicella-Zoster virus, Herpes simplex virus) occurred slightly more frequently in TYSABRI-treated patients than in placebo-treated patients. In post-marketing experience, there have been reports of serious cases of herpes infections, including very rare cases with a fatal outcome in patients treated with TYSABRI.

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%. 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. *Neurology*. 2014; Schippling. *Ann Neurol*. 2013). Symptoms of JCV GCN are similar to symptoms of PML (i.e.

cerebellar syndrome). In JCV GCN, serial MRI of the brain shows cerebellar atrophy 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 non-enhancing, hyperintense on T2-weighted MRI, without mass effect. The sub-cortical U fibres are characteristically involved.

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 once or twice. Use of an ultrasensitive PCR JCV DNA test is important (e.g., with a Limit of Detection (LoD) of at least 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 has been demonstrated to be a useful tool to investigate for possible PML (Whiteman, 1993) to support a clinical diagnosis. 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, indicating a rate of development of this disease of about 1/1000 patients (95% CI: 0.2-2.8) (Yousry, 2006). In the post-marketing setting, the risk of PML has been well characterized over the first four years of treatment with the identification of different levels of PML risk in different patient subgroups (see below).

2.7 *PML Risk Factors*

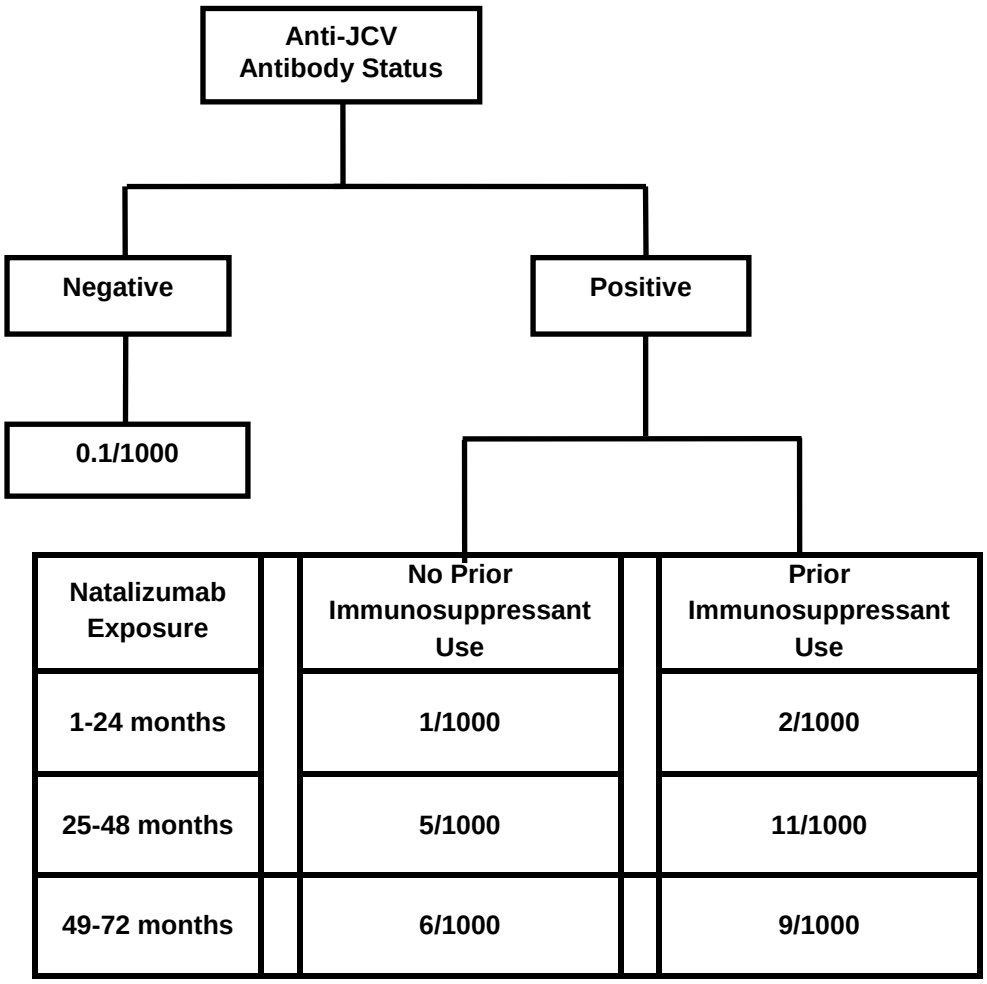
The following risk factors have been associated with development of PML during TYSABRI treatment:

- **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 two identified risk factors described below.
    - **Treatment duration**. In patients treated for more than 2 years, the risk of PML increases with increasing treatment duration.
    - **Prior immunosuppressant treatment**. Patients who have a history of treatment with an immunosuppressant prior to starting TYSABRI are also at increased risk of developing PML; the increased risk of PML associated with prior immunosuppressant use appears to be an additional risk factor to the TYSABRI treatment duration for more than 24 months.

Patients who have all three risk factors for PML (i.e., have received more than 2 years of TYSABRI therapy, **and** have received prior immunosuppressant therapy **and** are anti-JCV antibody positive) have a significantly higher risk of PML. In patients with all three risk factors, treatment with TYSABRI should only be continued after careful assessment and when the benefits outweigh the risks.

An estimate of the different levels of risk for PML in different patient subgroups is shown in Figure 1 below.

Figure 1: Estimated Incidence of PML Stratified by Risk Factor



The PML risk estimates are based on post-marketing data from approximately 125,000 TYSABRI exposed patients.
Data beyond 6 years of treatment are limited.

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

2.7.1 Testing for Anti-JCV Antibodies

Testing for serum anti-JCV antibody prior to initiating TYSABRI therapy or in patients who are already being treated with TYSABRI but who have not previously been tested provides additional information on the level of risk for PML. If a patient tests positive on any one occasion for anti-JCV antibody, they are considered to be at increased risk for developing PML, and do not need to be retested at a later date. Retesting of anti-JCV antibody negative patients should be considered every 6 months. A 6 month testing frequency would allow for earlier identification of patients who change serostatus from negative to positive compared to a 12 month testing frequency (based on data from the AFFIRM study [C-1801]). In the STRATIFY-1 clinical study, which prospectively collected and tested serum samples from Tysabri patients every 6 months, approximately 11% of patients changed serostatus from anti-JCV antibody negative to

positive per year. This would allow for more informed benefit-risk discussions regarding initiating or continuing treatment with TYSABRI.

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.

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 6.2 and Appendix 3: Alert Card, Appendix 4: Treatment Initiation and Continuation 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).

- The conduct of a pre-treatment cranial MRI scan as a reference is recommended, usually within 3 months before starting TYSABRI, and should be repeated on a yearly basis to update this reference. It may assist in differentiating PML lesions from MS plaques in patients that develop new neurological symptoms or signs once on therapy. 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.

- **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. Suspensions of TYSABRI therapy, for short duration (days or weeks), are not expected to compromise its effectiveness based on the pharmacodynamics of the drug.**

- The decision to suspend TYSABRI at any stage may be based on the initial clinical presentation, 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 2) describes a suggested approach to the clinical assessment of new or worsening neurological symptoms in MS patients treated with TYSABRI.

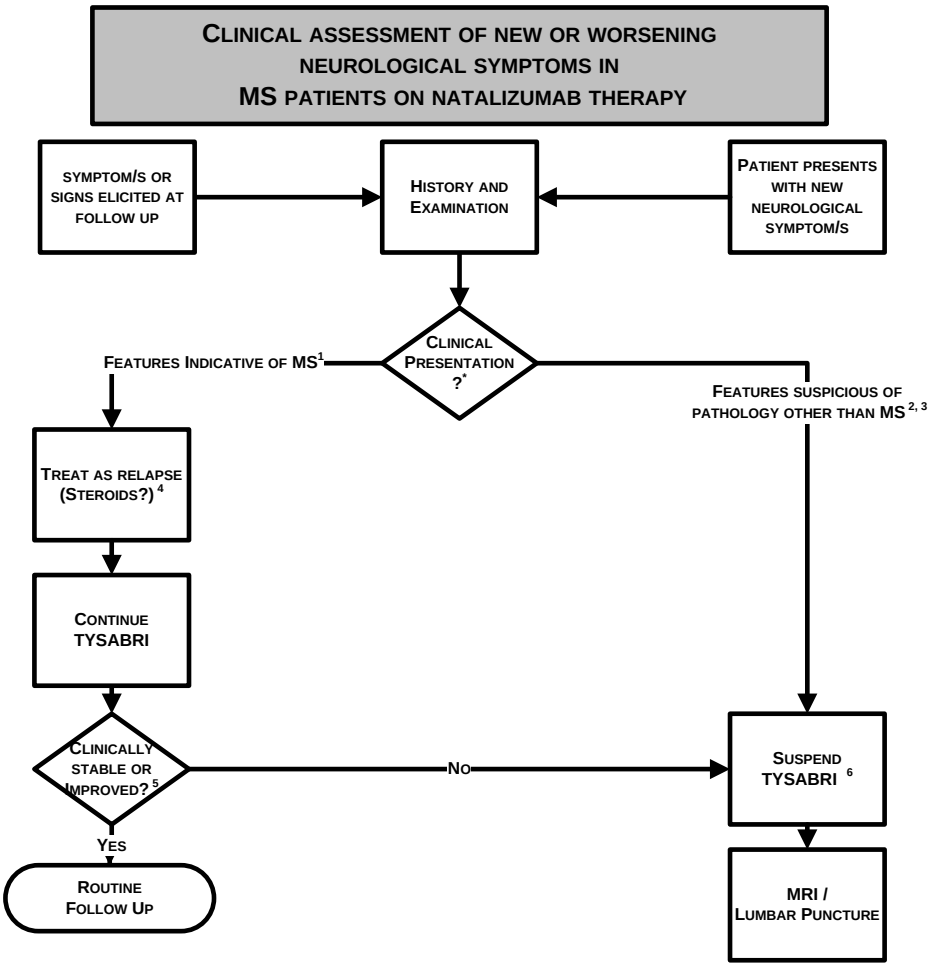
New or recurrent neurological symptoms should prompt careful evaluation in order to assess the underlying pathology e.g. MS or PML. Table 1 highlights the clinical features that help differentiate MS from PML. It should be noted that the table is not all inclusive and there may be a great deal of overlap 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 • Parathesia • Paraparesis • Optic Neuritis • Myelopathy	• Aphasia • Behavioural and neuropsychological alteration • Retrochiasmal visual deficits • Hemiparesis • Seizures

If the clinical presentation cannot exclude PML, further investigations to include MRI evaluation (Figure 3, Table 2) and / or lumbar puncture and cerebrospinal fluid (CSF) evaluation (Figure 4) 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 2. 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 standard MRI protocol preferably without and with contrast for the follow-up of patients on TYSABRI is proposed for the production of best possible images to assist with clinical decision-making (Yousry, et al. 2006). Such a protocol is widely used and publications are also available which show morphological changes in MRI sequences from patients treated with TYSABRI who have developed PML (Yousry, et al. 2012). Diffusion-weighted sequences may also be helpful in distinguishing MRI changes from a previous scan (Mader I, 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).

Suggested indications for a brain MRI:

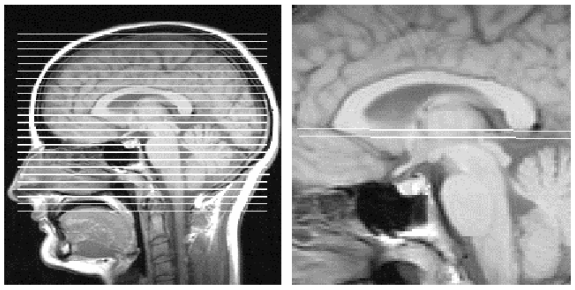
a) It is recommended to have a recent MRI (usually within 3 months) prior to initiation of TYSABRI as a reference, and that MRI be repeated on a yearly routine basis to update this reference. This may be helpful to differentiate PML from MS related symptoms in patients that develop new or worsening neurological symptoms or signs once on therapy.
b) Unexpected clinical worsening/suspicious clinical course (Figure 2)

The MS MRI protocol can take >30 minutes, so comfortable positioning is recommended. Repositioning of any follow-up scans to the same anatomical landmarks is essential for a good comparison. A copy of each evaluation should be retained (electronically archived) for subsequent evaluation if clinically indicated.

Standard cranial MRI protocol for all scans:

- Scanner field strength ≥1.0 T Slice thickness ≤5 mm and no gap
- whole brain coverage
- Scan orientation on the sub-callosal line (three-plane localiser)

Sagittal **Sagittal magnified**



Sequences recommended

- Sagittal FLAIR
- Axial TSE PD/T2
- Axial FLAIR
- Axial diffusion-weighted
- Axial SE T1 pre and post contrast
  - Gd injection 0.1 mmol/kg over 30 seconds
  - > 5-minute delay after contrast injection

Recommendations for MS MRI sequences:

- T2: TR 2800–3800 ms
  Short: TE 14–45 ms, long TE 80–120 ms
- T1: TR 500–650 ms

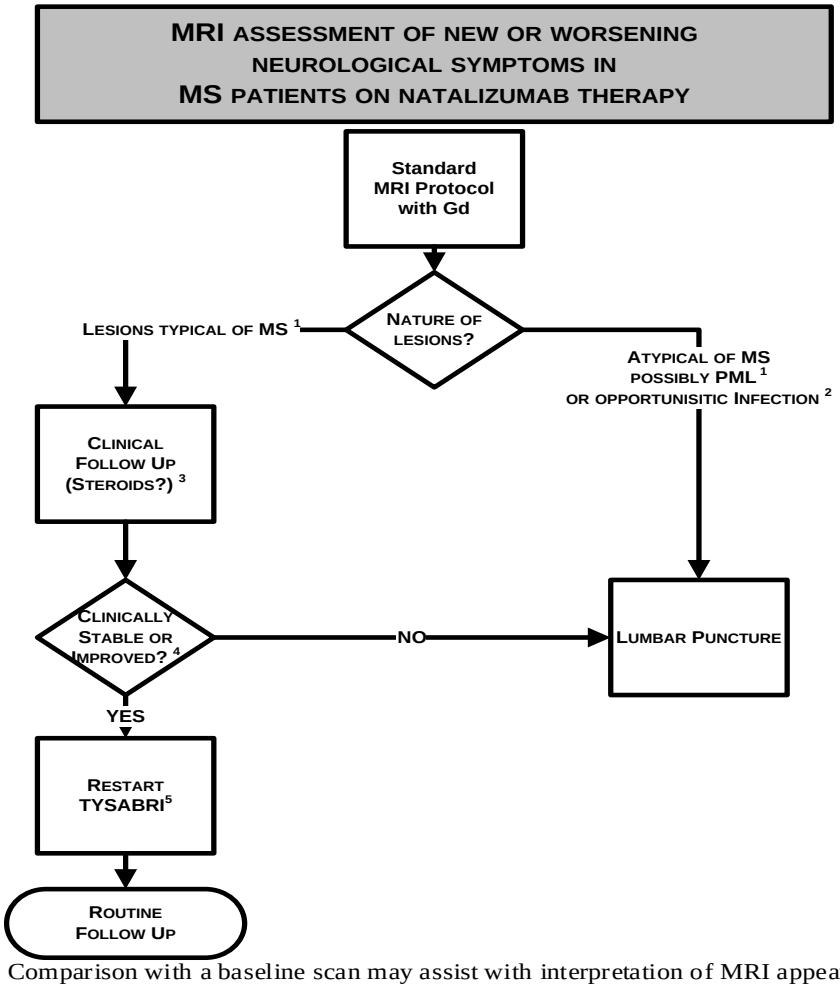
TE 10–20 ms

- FLAIR: TR 7000–9000 ms
  TE 100–160 ms, TI 2,500 ms

Further information on the differentiation between PML and MS may be found at www.ms-pml.org or may be requested by sending an email to safeguardAC@vumc.nl.

Figure 3. 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.
(It should be noted that none of the MRI features are pathognomonic of MS or PML)

Feature	Multiple Sclerosis	Progressive Multifocal Leukoencephalopathy
Aspect and location of new lesions	Focal, generally periventricular in location. Lesions occur in all areas of the brain particularly the corpus callosum and spinal cord.	Diffuse. Generally large >3cm lesions in a unifocal, multifocal or widespread distribution. Subcortical location rather than periventricular. Affecting U fibers and extending into the gyrus. Cortical GM involvement in 50% of cases. Posterior fossa less frequent site. Spinal cord presentation rare.
Borders	Sharp edges; mostly round or flame shaped (especially periventricular lesions), confluent with other lesions; U-fibers may be involved.	Irregular in shape. Ill-defined border toward the white matter, sharp border toward the cortical grey matter.
Mode of extension	Initially focal, lesions enlarge within days or weeks and later decrease in size within months.	Lesion volume increases continuously, and often rapidly to contiguous (multifocal) and non-contiguous regions (widespread).
Mass effect	Large acute lesions may have mass effect.	No mass effect even in large lesions.
On T2-weighted sequence	Homogeneous hyperintensity.	Diffuse hyperintensity, irregular signal intensity within the lesions, can have a punctate microcystic appearance. Small punctate T2 lesions may be seen in proximity to the lesion.
On T1-weighted sequence	Acute lesions: hypointense (due to edema) or isointense. Increasing signal intensity over time in 80 percent; decreasing signal intensity (axonal loss) in about 20 percent.	Slightly hypointense at onset, with signal intensity decreasing over time in the affected area; no reversion to isointense signal intensity.
On FLAIR sequence	Hyperintense, sharply delineated.	FLAIR is the preferred sequence for PML diagnosis, because of the subcortical location.
Contrast enhancement	Acute lesions: homogeneous nodular or ring enhancement, with sharp edges eventual resolution over 1-2 months. Chronic lesions: no enhancement.	Less than half of the cases to date have shown some enhancement at the time of presentation often with a patchy or punctate appearance. Rim enhancement at leading edge can be seen.
Diffusion weighted imaging	Acute lesions hyperintense. Chronic lesions isointense. Conforms to shape of lesions on FLAIR and T2W.	Acute PML lesions are hyperintense but not specific for PML. Helpful to detect new PML lesions within confluent areas of chronic WM disease. ADC maps not helpful.
Atrophy	Focal atrophy possible, due to focal white-matter degeneration; no progression.	No focal atrophy but atrophy in late stages of PML progression.

(Reference: Kappos, 2011; Yousry, 2012)

3.4 *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 3).

The detection of JCV DNA by PCR in the cerebrospinal fluid of a symptomatic patient 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 less sensitive than the recommended 10 copies/mL (see below), and clinical and MRI suspicion remains high.

Cerebrospinal Fluid (CSF) by lumbar puncture (LP):

Follow the local standard technique for LP. Collect required fluid for routine CSF analysis (e.g. glucose, protein and cell count). Submit the sample for routine analysis to the local laboratory in accordance with local procedures. An additional 5mL of CSF for JCV DNA detection by PCR analysis should be collected, in order to ensure that at least 2mL are available for analysis.

Suggested procedure for CSF preparation for PCR analysis:

- Using a disposable pipette aliquot at least 1 mL of CSF for JCV PCR analysis into 2 cryovials (e.g. Nunc plastic screw top containers)
- Record subject identification, sample type (i.e. CSF) and date sample was collected on each vial
- CSF samples sent for DNA analysis should be as free of blood as possible and preferably from the last tube collected. The first tube collected should not be used for DNA unless it is the only sample available.
- If the sample is contaminated with blood, please indicate on the vial and on the form accompanying the sample to the analysis laboratory
- Freeze the sample at -20°C or –70°C immediately after it is drawn (do not refrigerate)*
- Ship two vials to the laboratory (info to be provided) keeping the additional sample as back-up
- All additional samples should be kept frozen at -70°C in case additional samples or testing is required

Freezing should be done as soon as possible following collection. If immediate freezing is not possible, samples should be kept at 4°C (max. 24 hours) until freezing is possible.

*Specimen stability (Unilabs): frozen at -20°C for 7 days; frozen at -70°C for 30 days.

*Specimen stability (Focus): room temperature 48 hours; refrigerated 7 days; frozen 30 days.

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.

Reference testing laboratories are Unilabs, Denmark.
Helpline: +45 3374 3077 (Opening Hours 08:00-16:30 CET);
Email: helpdesk@unilabs.com

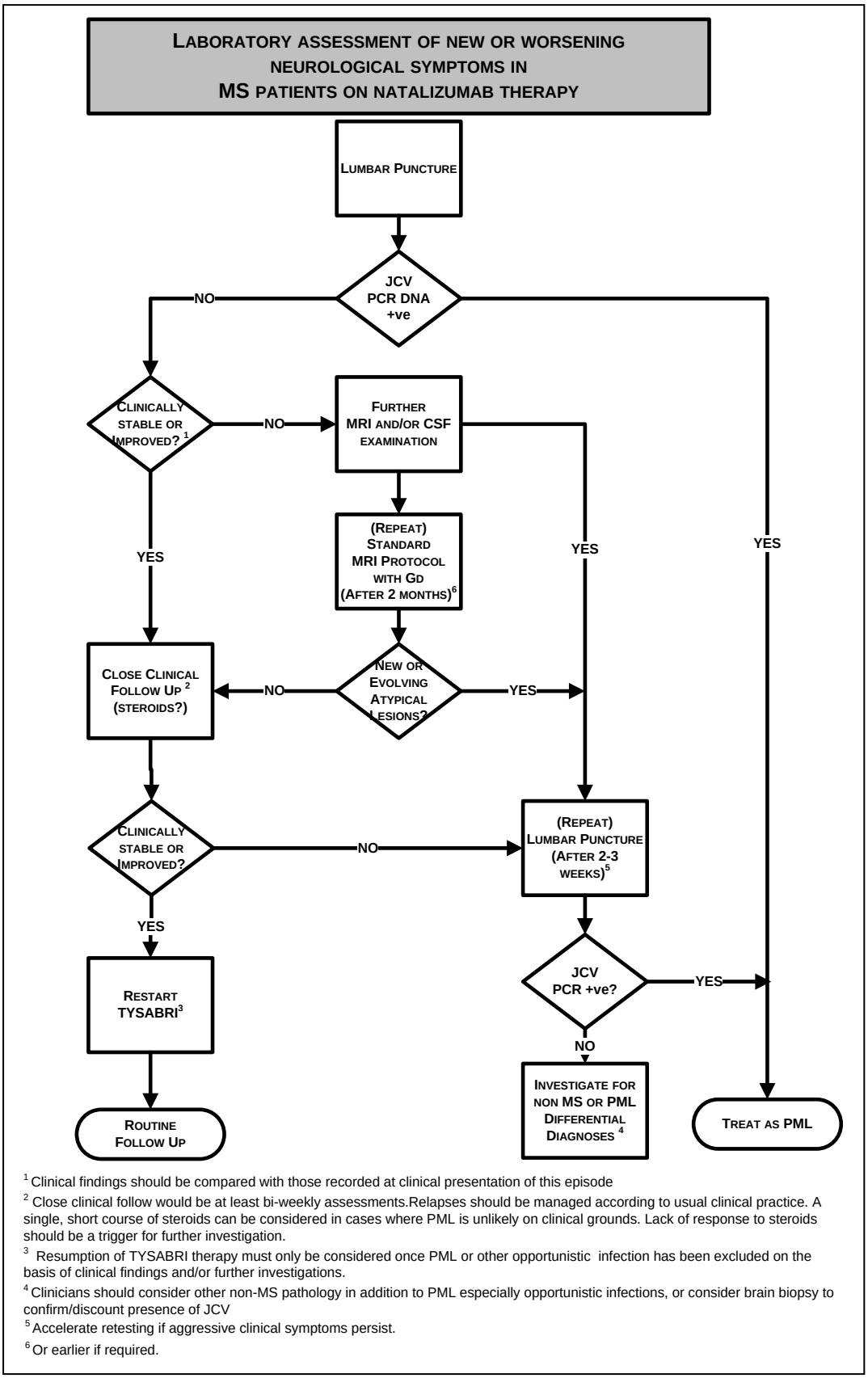
If continued clinical or MRI-based suspicion of PML persists despite a local or reference laboratory result being negative (i.e. not detected) for JCV DNA by PCR, and especially if the result is based on an assay with a LoD that is less sensitive than the recommended 10 copies/mL, a further test for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

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 transport of samples to the central facility are available from Medical Affairs in your country.

Figure 4. 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.

Reference: Kappos et al, 2011

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 may lead to immune reconstitution which in this case contributed to the survival of the MS patient reported by Langer-Gould and colleagues (2005). Hence, the effect of plasma exchange 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% seen in earlier studies in which measurements occurred after drug discontinuation over a similar period of observation. These data also suggested that additional plasma exchanges (up to a total of 5 over a 10 day period) would be required to more consistently reduce natalizumab concentrations to below sub-therapeutic levels. This may be helpful to reconstitute immunocompetence more quickly in the brain and therefore possibly assist in the stabilisation of PML. 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 cranial 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 1.5mg/kg/d x 2 wks with taper over 2 months

2) Intravenous methylprednisolone (1g/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, stopping TYSABRI therapy, and the use of plasma exchange (PLEX) may have improved the outcome of PML in affected TYSABRI patients.

Of the 395 postmarketing PML cases reported as of 06 August 2013, 132 cases were from clinical or observational studies, and 263 cases were reported spontaneously. The survival rate for confirmed postmarketing patients with PML is 77% (303 of 395 patients are alive), and the mortality rate is 23% (92 of 395 patients died).

As of 05 June 2013, 30 of 372 confirmed PML cases (8.1%) were clinically asymptomatic at the time of PML diagnosis and were initially identified by MRI. Follow-up was available for 19 of the 30 cases with a mean and median duration of follow-up of 16 months (range 4.8 to 27.3 months). The other 11 cases either had not yet reached the 6-month follow-up timepoint (n = 8) or were lost to follow-up (n = 3). The majority (11/19, 58%) of the asymptomatic patients who were available for follow-up remained free of clinical symptoms over the 16 months (mean 15.2 months; median 14.2 months) of follow-up. Eight of the 19 patients (42%) later developed clinical symptoms after PML diagnosis (most frequently cognitive/behavioral symptoms). One patient who developed clinical symptoms did not have a symptom onset date available. For the other 7 patients, the mean time to onset of symptoms (defined as the time from first suspect MRI to the onset of initial clinical symptoms) was 38 days (median 20 days, range 1 to 130 days). The mean and median follow-up time for the patients who developed clinical symptoms was 17.5 and 17.6 months, respectively.

Asymptomatic PML patients had a shorter time from suspicion of PML to diagnosis of PML compared to symptomatic PML patients. In addition, asymptomatic PML patients had a higher proportion of unilobar PML lesions on MRI at the time of diagnosis compared to symptomatic PML patients.

6 Adverse Reactions associated with infusions

6.1 *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.

6.2 *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.

6.3 *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.

6.4 *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 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. Since patients who have received

an initial short exposure to TYSABRI and then had an extended period without treatment are more at risk for hypersensitivity upon redosing, the presence of antibodies should be evaluated before start of re-dosing and if these remain positive in a confirmatory test after six weeks, treatment should not be resumed.

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
www.i-med.ac.at/neurologie/patienten/liquor.html

7 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 TYSABRI after 24 months, especially the increased risk of PML, and should be instructed together with their caregivers on early signs and symptoms of PML. Template treatment initiation and continuation forms are provided in Appendix 4.

7.1 *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 5.1, 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.

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/ 203, level 3 Rue D'Argens Gzira GZR 1368, Malta
E: postlicensing.medicinesauthority@gov.mt

7.2 *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 in case side effects including PML occur 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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9 Appendices

Appendix 1. Summary of Product Characteristics (SmPC)

Appendix 2. Patient Information Leaflet (PIL)

Appendix 3. Patient Alert Card

Appendix 4. Treatment Initiation and Continuation Forms

To be inserted when finalised