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

Version 9.0 for Singapore

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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 magnetic resonance imaging (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 Package Insert (PI) [Appendix 1] and is supported by the Treatment Initiation Form, Treatment Continuation Form, and Treatment Discontinuation Form (Appendix 4). This guidance provides additional risk mitigation measures; for primary guidance, please see the PI.

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

Physicians intending to prescribe TYSABRI for the first time will be expected to complete a Letter of Undertaking acknowledging the risks associated with using TYSABRI (Appendix 5). Furthermore, a Pre-Infusion Questionnaire should be completed prior to each individual infusion and is included in Appendix 6. Finally, PML Data Collection Forms, which should be used wherever possible to collect follow-up data on patients with Progressive Multifocal Leukoencephalopathy (PML), are also included in the physician pack (Appendix 7).

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

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

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

2 Opportunistic Infections Including PML

Prescribers should be aware of the possibility that PML and other opportunistic infections may occur during TYSABRI therapy and should include these events in the differential diagnosis of all infections that occur in TYSABRI-treated patients. Cases of PML have also been reported in patients up to 6 months after the last dose of TYSABRI. Patients and their partners and caregivers also need to be advised of symptoms that may be indicative of early PML and continue to be vigilant for approximately 6 months after discontinuation (see Section 3.2, Appendix 3, and Appendix 4).

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

2.1 *Definition*

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

2.2 *Herpes Infections*

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

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

2.3 *Progressive Multifocal Leukoencephalopathy*

2.3.1 Epidemiology

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

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

adults that used similar methodologies [Egli 2009; Kean 2009; Knowles 2003; Stolt 2003]. In general, anti-JCV antibody prevalence did not appear to be affected by prior IS use, prior exposure to TYSABRI, or duration of TYSABRI exposure.

2.3.2 Aetiology

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

2.3.3 Pathology

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

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

2.3.4 PML in TYSABRI-Treated Patients

During extended preregistration trials, 2 cases of PML were reported in patients with MS and a full safety evaluation revealed 1 additional case in a clinical trial patient with Crohn's disease [Yousry 2006]. In the postmarketing setting, the risk of PML has been well characterised over the first 6 years of treatment with the identification of different levels of PML risk in different patient subgroups (see Section 2.3.5).

2.3.5 PML Risk Factors

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

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

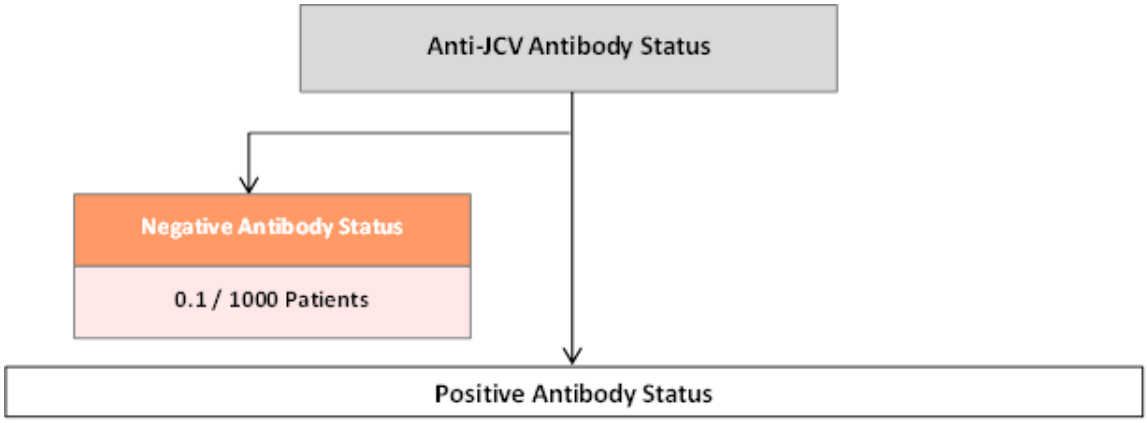
Patients who have all 3 risk factors for PML (i.e., are anti-JCV antibody positive, have received more than 2 years of TYSABRI therapy, and have received prior IS therapy) have a higher risk of PML. In anti-JCV antibody-positive TYSABRI-treated patients who have not used prior IS therapies, the level of anti-JCV antibody response (index) is associated with the level of risk for PML (i.e., the risk is greater in those with a high antibody index compared with those with a low index). Currently available evidence suggests that the risk of PML is low at an index equal to or below 0.9 and increases substantially above 1.5 for patients who have been receiving treatment with TYSABRI for longer than 2 years [Ho 2017].

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

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

- For anti-JCV antibody-negative patients: PML risk estimates are based on postmarketing data from approximately 125,000 TYSABRI-exposed patients where the estimated incidence of PML for anti-JCV antibody-negative patients is 0.1/1000. Anti-JCV antibody-negative patients may still be at risk of PML for reasons such as a new JCV infection, fluctuating antibody status, or a false-negative test result.
- For anti-JCV antibody-positive patients: Risk estimates were derived using the Life Table Method based on the pooled cohort of 21,696 patients who participated in the STRATIFY-2, TOP, TYGRIS, and STRATA clinical trials. The risk estimates from the Life Table Method are forward-looking in yearly intervals (for example, the risk estimate corresponding to the 25- to 36-month TYSABRI exposure period is the PML risk estimated for the next year for patients treated for 24 months with TYSABRI). The individual treatment length of each patient is taken into consideration with drop-outs (e.g., treatment discontinuation) accounted for.
- For anti-JCV antibody-positive patients who have not used prior IS therapies: The index can further stratify PML risk in patients treated with TYSABRI. A higher anti-JCV antibody index is associated with an increased risk of PML.
- For anti-JCV antibody-positive patients who have used IS previously: These patients are at an increased risk of PML because prior IS use is recognised as an independent risk factor for PML. PML risk estimates for this patient population are based on TYSABRI clinical trial data where prior IS use comprised the following 5 IS therapies: mitoxantrone, methotrexate, azathioprine, cyclophosphamide, and mycophenolate mofetil. The exact mechanism by which these 5 IS therapies lead to an increased PML risk is unknown. In patients with prior IS, current data do not show an association between higher index and PML risk. The underlying biological explanation for this effect is unknown.

Figure 1: PML Risk Estimates Algorithm



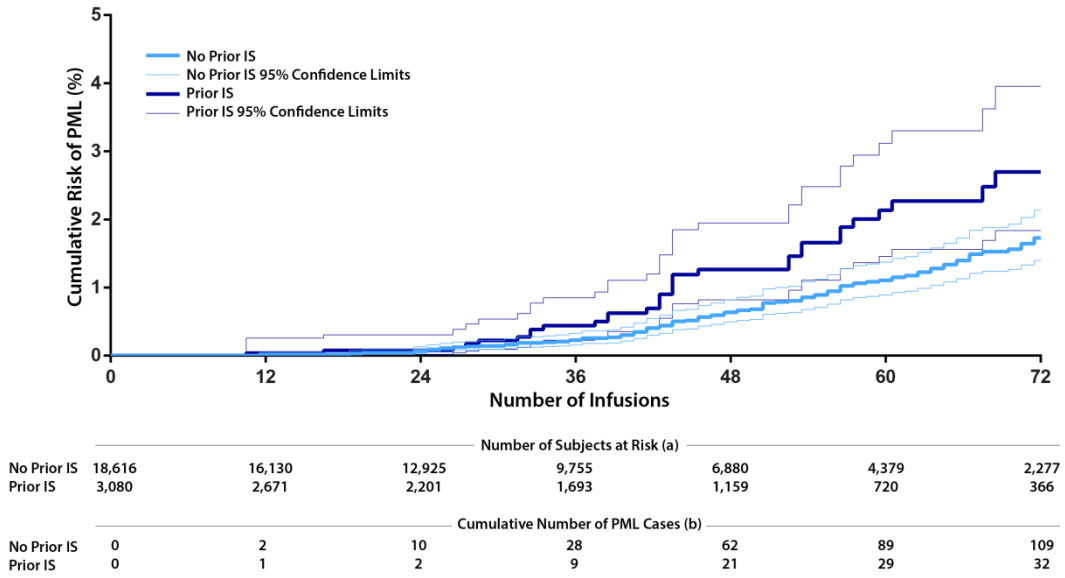
Natalizumab Exposure	PML risk estimates per 1000 patients				
	Patients without prior IS use				Patients with Prior IS use
	No index value	Antibody Index ≤ 0.9	Antibody Index > 0.9 ≤ 1.5	Antibody Index > 1.5	
1-12 months	0.1	0.1	0.1	0.2	0.3
13-24 months	0.6	0.1	0.3	0.9	0.4
25-36 months	2	0.2	0.8	3	4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

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

Additionally, some physicians may find a Kaplan-Meier (KM) curve useful to provide a visual representation of cumulative PML risk over time using a time-to-event analysis (Figure 2). In the KM curve, PML risk estimates for a given timepoint represent the total cumulative risk up to that timepoint (for example, at the timepoint of 48 months, the risk estimate on the KM curve represents the total risk up to 48 months, not the risk between 24 months and 48 months). Like

Figure 1, data for these analyses were also obtained from the pooled cohort of 21,696 patients who participated in the STRATIFY-2, TOP, TYGRIS, and STRATA clinical trials and also take the individual treatment length of each patient into consideration with drop-outs (e.g., treatment discontinuation) into account.

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



	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

IS = immunosuppressant; JCV = John Cunningham virus; PML = progressive multifocal leukoencephalopathy.
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 is used to impute the status. (a) Average number of subjects who were in the study and did not have the event at the end of the specified time over multiple imputations. (b) Cumulative number of PML cases at the end of the specified time.
Source: TYSABRIMS/PRAC-ART20/POOLED/F-TTPML-KM-PRIORIS-MI5-V2-SAS

2.3.6 Extending the Dosing Interval for PML Risk Mitigation

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

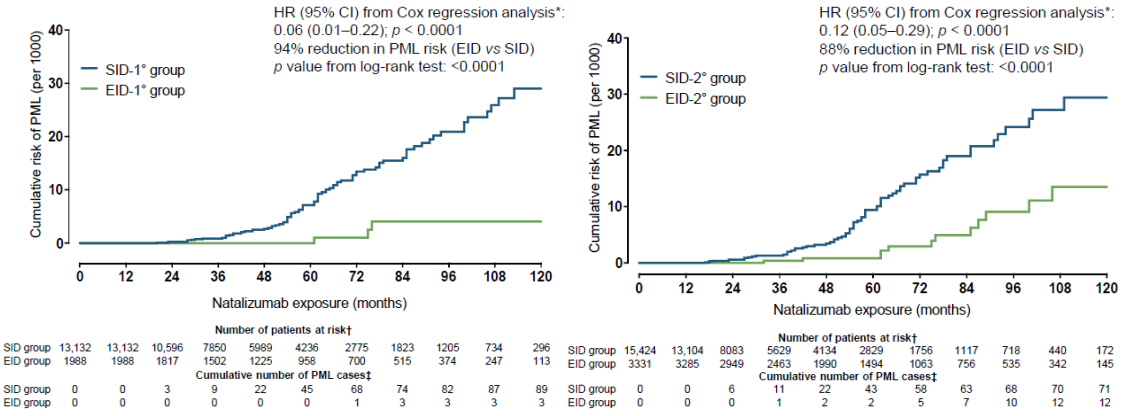
Current real-world data support that there is a significant reduction in the risk of PML in anti-JCV antibody-positive patients treated with an average TYSABRI dosing interval of approximately 6 weeks compared with the approved dosing regimen, which is every 4 weeks (refer to the PI Section 5.1 [Pharmacodynamic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

Summary results from real-world data on extended interval dosing

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

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

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



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

Results from efficacy modelling data

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

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

2.3.7 Recommended Patient Monitoring

2.3.7.1 Testing for Anti-JCV Antibodies

Testing serum for anti-JCV antibodies provides supportive information for risk stratification of TYSABRI therapy. Testing for serum anti-JCV antibodies prior to initiating TYSABRI therapy or in patients receiving TYSABRI with an unknown antibody status is recommended. Anti-JCV antibody-negative patients may still be at risk of PML for reasons such as a new JCV infection, fluctuating antibody status, or a false-negative test result. Retesting of anti-JCV antibody-negative patients and low index patients who have no history of prior IS use every 6 months once they reach 2 years of treatment is recommended to inform on appropriate patient MRI monitoring.

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

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

For technical questions regarding STRATIFY JCV, please contact Unilabs, Denmark at +45 3374 3077 (Hours: 8:00 -16 :30 CET), Email: Helpdesk@unilabs.com

For further information, please contact Head of Marketing, Singapore at +65 6296 6977.

2.3.7.2 Recommended MRI Monitoring for Early Detection of PML

In the clinical practice, MRI has been shown to be a useful tool for monitoring patients with MS. It may assist in differentiating PML lesions from MS plaques in patients who develop new neurological symptoms or signs once on therapy. Frequent MRI surveillance in patients at high risk of PML may lead to an earlier diagnosis of PML and better clinical outcomes [Prosperini 2016; Scarpazza 2019; Wattjes 2015]. Recommendations for MRI monitoring are summarised below:

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

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

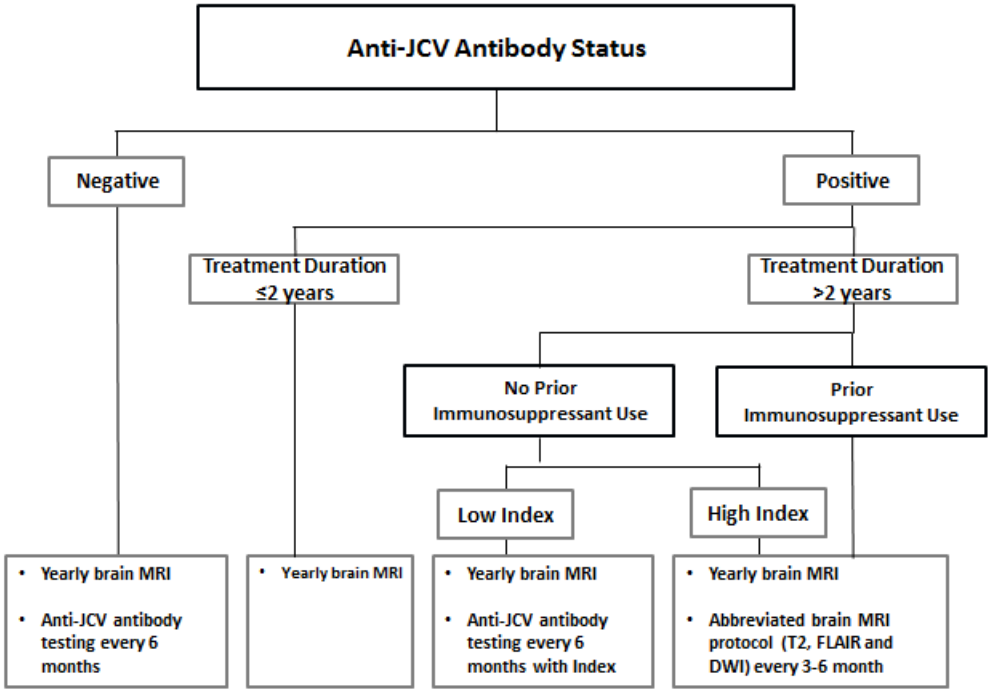
  or

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

Current evidence suggests that the risk of PML is low at an index equal to or below 0.9 and increases substantially above 1.5 for patients who have been receiving treatment with TYSABRI for more than 2 years. MRI monitoring decisions should take this evidence into consideration, and physician discretion is advised for those patients with index values between 0.9 and 1.5.

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

Figure 4: Recommended Patient Monitoring



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

Table 1: MRI Protocols

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

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

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

If MRI lesions suggestive for PML are detected, the full MRI protocol should be extended to include contrast-enhanced T1-weighted imaging to detect inflammatory features and the possible coincidence of PML and PML-immune reconstitution inflammatory syndrome (IRIS), particularly during follow-up. It is also recommended

that upon request for follow-up MRI, treating physicians inform radiologists that PML or other opportunistic infections are being considered in the differential diagnosis.

2.3.8 Diagnosis of PML

The American Academy of Neurology-published consensus statement on PML diagnostic criteria requires clinical, radiographic, and virologic findings or typical histopathological findings and the presence of JCV [Berger 2013]. These former criteria obviate the need for a brain biopsy but require compatible clinical and MRI findings plus detection of JCV DNA in the cerebrospinal fluid (CSF) by polymerase chain reaction (PCR) for a definite PML diagnosis; however, based on an alternative classification system, physicians are advised that in TYSABRI-treated patients with MS, diagnosis of PML can be considered confirmed in the absence of clinical symptoms [Dong-Si 2012; Dong-Si 2014] (see Section 2.3.8.4).

Any case of PML should be reported to the Vigilance and Compliance Branch, Health Products Regulation Group, Health Sciences Authority (HSA) at Tel: 6866 1111, fax: 6478 9069, or report online at https://www.hsa.gov.sg/adverse-events

2.3.8.1 General Principles

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

Patients and their partners and caregivers need to be advised of symptoms that may be indicative of early PML (see Section 3.2, Appendix 3, and Appendix 4) and be counselled on the need to be vigilant for these symptoms while the patient is receiving TYSABRI therapy, and also for approximately 6 months after the last dose of TYSABRI (PML has been reported up to 6 months after the last dose of TYSABRI in patients who did not have findings suggestive of PML at the time of discontinuation).

In all cases where further investigation of change in neurological status or change in brain MRI is indicated, TYSABRI must be suspended and not restarted until non-MS pathology has been confidently excluded. Suspension of TYSABRI therapy for a short duration (days or weeks) is not expected to compromise therapeutic efficacy based on the PD of the drug (see Section 2.3.6). TYSABRI dosing should only be restarted when the diagnosis of PML is confidently excluded (if necessary, by repeating clinical, MRI and laboratory investigations if suspicion of PML remains).

- **All suspected cases of PML should be assessed using the PML Data Collection Form (Suspect). The clinical and functional outcomes of all confirmed cases of PML should be followed up using the PML Data Collection Form (Month 3, Month 6, Month 12, and Month 24) (appendix 7)**

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

2.3.8.2 Clinical assessment

Any new or recurrent neurological symptoms should prompt careful evaluation in order to ascertain the underlying pathology, and in a patient with MS disease control, such changes warrant a clinical suspicion of PML (or other opportunistic infection). It is important to note that the presence of new onset neurologic symptoms is not required to diagnose PML (in the setting of other confirmatory evidence) and cases of asymptomatic PML have been reported. In both high- and low-risk asymptomatic patients, any new suspected lesion at a recommended MRI evaluation for monitoring PML risk should be carefully evaluated, particularly when an abbreviated protocol has been performed (see Section 2.3.8.3). Table 2 highlights the clinical features that may help differentiate MS from PML. It should be noted that the table is not all inclusive and that there may be a great deal of overlap between symptoms of the 2 conditions. **Physicians should be aware that the clinical features of PML or other opportunistic infections can be difficult to distinguish from MS, especially early in the evolution.** The history and pattern of previous and current symptoms and signs are important to note and will facilitate the management of TYSABRI-treated patients.

Table 2: Clinical Features of MS and PML

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

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

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

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

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

2.3.8.3 MRI Differentiation Between PML and MS Relapse

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

Table 3: Features Visualised on MRI

The table shows features to be considered in the differential diagnosis of MS and PML

Feature	MS	PML
Lesion location	Focal, periventricular, or deep white matter. Lesions occur in all areas of the brain, optic nerves, and spinal cord.	Asymmetric, focal, or multifocal. Subcortical or diffuse white matter, cortical grey matter, and deep grey matter, brainstem, middle cerebellar peduncles. PML is not seen in spinal cord or optic nerves.
Lesion shape and lesion borders	Ovoid or flame shape; sharp borders, often perilesional oedema.	Irregular shape, finger-like projections toward the cortex. Ill-defined border toward the white matter, sharp border toward the grey matter.
Mode of extension	Initial enlargement over days or weeks and decrease in size within months.	Progressive increase in size.
Mass effect	Large acute lesions may have mass effect.	No mass effect.
T2-weighted images	Homogeneous hyperintensity with surrounding oedema.	Diffuse hyperintensity often with punctate microcystic inclusions. Perilesional nodules in the vicinity of the primary lesion (milky way galaxy).

Feature	MS	PML
T1-weighted images	Acute lesions: hypointense or isointense. Increasing signal intensity over time.	Isointense to hypointense at onset with decreasing signal intensity over time.
FLAIR images	Hyperintense, sharply delineated.	Hyperintense. Most sensitive sequence for detection of PML.
Contrast enhancement in acute lesions	Homogeneous nodular, ring or open ring enhancement conforms to shape and size of the lesion. Resolution over 1-2 months.	43% of lesions show enhancement at the time of presentation. Patchy or nodular appearance. Enhancement does not conform to size or shape of the lesion. Increased enhancement with IRIS.
DWI	Acute lesions hyperintense. Chronic lesions isointense.	Acute lesions hyperintense. Distinguishes new PML lesions within areas of chronic white matter disease. No restriction on ADC.
Atrophy	Diffuse atrophy with progressive MS disease.	Post PML-IRIS – encephalomalacia and diffuse brain atrophy in the affected areas.

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

2.3.8.4 Laboratory Investigation

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

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

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

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

For details of the procedure for the collection, handling and transport of samples to the central facility, please contact Head of Marketing, Singapore at +65 6296 6977.

2.3.9 Management of PML

Immune reconstitution

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

Rapid removal of TYSABRI from the body using PLEX and/or immunoadsorption (IA) has also been reported with the intention of accelerated restoration of CNS immunosurveillance [Calabrese 2011; Clifford 2015; Clifford 2010; Dahlhaus 2013; Fernández 2013; Ghezzi 2011; Grebenciucova and Berger 2018; Hellwig and Gold 2011; Kappos 2011]. It has been recommended that the need for PLEX should be carefully considered and, if used, that patients should be closely monitored for the development of IRIS (see Section 2.3.9.1), which occurs in almost all patients treated with PLEX for TYSABRI-associated PML and appears to occur more rapidly than in patients who are not treated with PLEX [Carruthers and Berger 2014; Clifford 2010]. Based on a retrospective analysis of natalizumab-treated patients since its approval, no difference was observed on 2-year survival after PML diagnosis between patients who received PLEX and those who did not. Physicians should use medical judgement when considering the use of PLEX to treat PML [data on file].

Antivirals and other adjuvants

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

Mirtazapine is a 5HT2A serotonin receptor antagonist that is widely used to treat psychiatric disorders. In vitro studies have shown that JCV uses the 5HT2A serotonin receptor and sialylated oligosaccharides for entering the cell [Elphick 2004; Maginnis 2015; Neu 2010], and 5HT2A serotonin receptor antagonists can inhibit JCV infection in human glial cells [Elphick 2004]. Therefore, mirtazapine has been used for treatment of PML on the basis that it might prevent the spread of the virus. However, there is also in vitro evidence that PML-mutant and wild-type JCV strains utilise alternative nonsialylated pathways to infect cells [Geoghegan 2017]. As with mefloquine, anecdotal reports have suggested a benefit of mirtazapine in TYSABRI-associated PML treatment [Calic 2015; Clifford 2010; Fabis-Pedrini 2016; Gheuens 2012; Lauda

2015; Lindå and von Heijne 2013; Schröder 2010; Wenning 2009]. However, benefit could not been confirmed in retrospective analyses [Blankenbach 2019; Stefoski 2019; Tan 2011], although the authors of 1 analysis [Jamilloux 2016] suggested that mirtazapine may increase survival in TYSABRI-associated PML based on an increased 1-year survival rate in 16 patients treated with mirtazapine compared with a previously reported 1-year survival rate in 336 patients where mirtazapine treatment was not assessed [Dong-Si 2015].

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

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

2.3.9.1 Treatment of Immune Reconstitution Inflammatory Syndrome

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

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

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

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

Prophylactic steroid treatment is currently not recommended [Antoniol 2012; Scarpazza 2017a; Stefoski 2019; Tan 2011]. As scientific and medical knowledge, including both

diagnostic criteria and management of IRIS is rapidly evolving, please contact Medical Affairs in your country for the most up-to-date information on treatment recommendations.

Other treatments

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

Intravenous immunoglobulins have also been used to try to slow and treat IRIS in patients with TYSABRI-associated PML. However, data are limited to only a few case reports, and clinical outcomes have been inconsistent [Calic 2015; Clifford 2010; Kuhle 2011; Lauda 2015; Thaker 2014].

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

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

2.3.10 Prognosis

Improved survival from PML after TYSABRI therapy has been associated with a younger age at PML diagnosis, less functional disability before PML diagnosis, a lower JCV load at PML diagnosis, and more localised brain involvement on MRI at diagnosis [Dong-Si 2015]. Furthermore, asymptomatic patients at PML diagnosis have been reported to have better survival and less functional disability than symptomatic patients at PML diagnosis [Dong-Si 2014; Prosperini 2016]. For information on outcomes associated with PLEX, see Section 2.3.9.

Asymptomatic PML (with a comparison to symptomatic PML)

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

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

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

2.3.11 PML Diagnosed After Discontinuation of TYSABRI

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

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

3 Educational Guidance

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

3.1 *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 part of this pack (Appendix 2) so that the physician can become familiar with the PIL prior to counselling patients about TYSABRI therapy.

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

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

In addition, locally agreed templates for a Treatment Initiation Form, a Treatment Continuation Form at 24 months of treatment, and a Treatment Discontinuation Form describing specifically the risk of PML with TYSABRI therapy and the importance of monitoring for PML are provided in Appendix 4. These should be provided to and discussed with patients before initiation of treatment, after 24 months of treatment, and after discontinuation to ensure that patients are fully informed about the risk of PML. The physician should keep 1 copy of these forms and 1 copy should be given to the patient.

3.2 *Patient Alert Card*

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

It reminds patients that because of the risks of PML associated with TYSABRI, they must contact their physician if they believe that either their MS is getting worse or they or their family members notice new symptoms such as changes in mood, behaviour, memory, motor weakness, speech, or communication difficulties. Partners and caregivers should also be made aware of the information provided in the Patient Alert

Card. The Patient Alert Card includes a recommendation for patients to retain the card for a period of 6 months after the last dose of TYSABRI therapy because signs and symptoms suggestive of PML may occur up to 6 months after discontinuation and patients and their partners and caregivers should report any suspect changes in neurological status during this time.

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

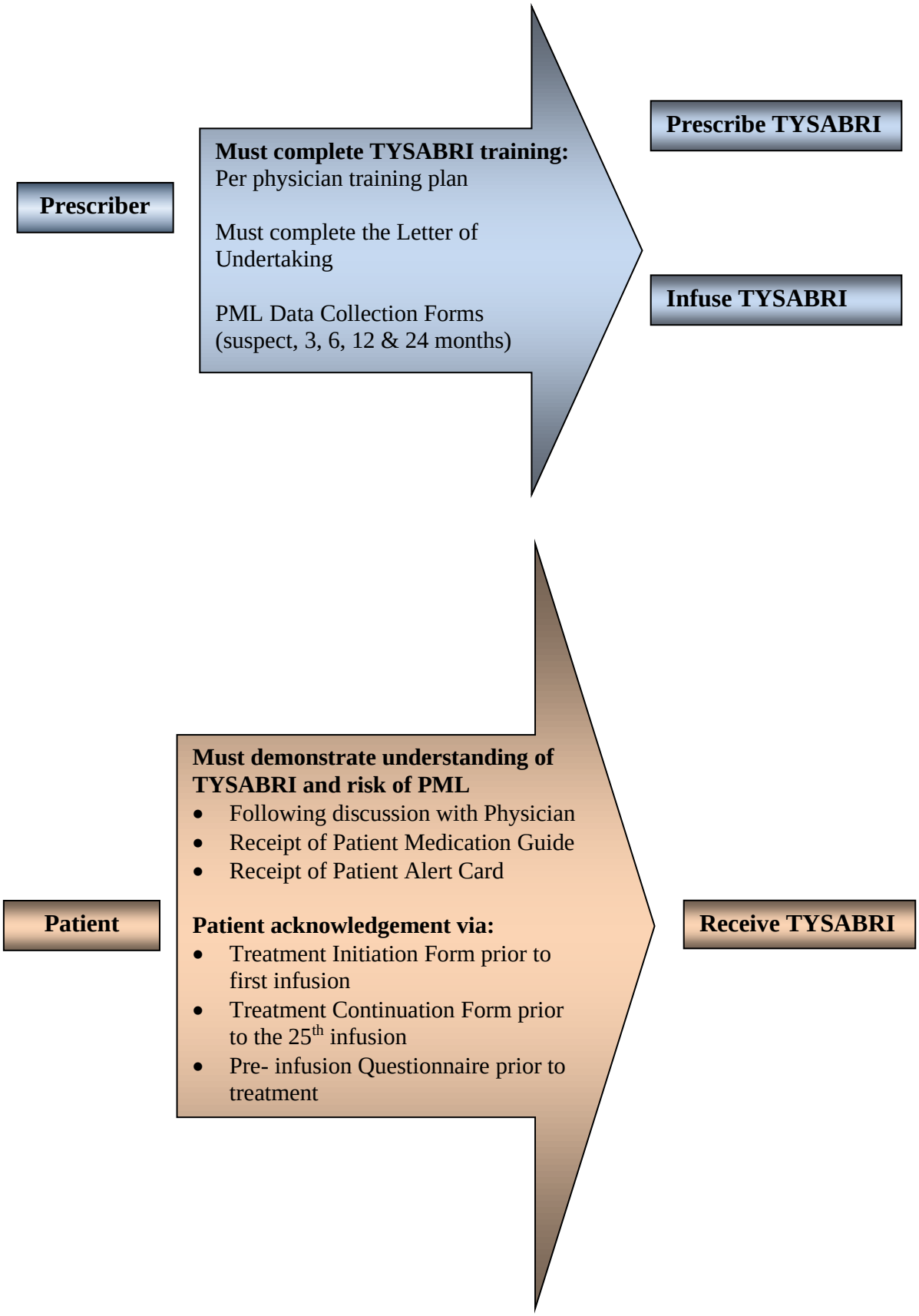
Patient Alert Cards (see Appendix 3) are included as part of the Physician Pack. Additional cards can be ordered from the local company office.

For further details, please contact Head of Marketing, Singapore at +65 6296 6977.

Fax: +65 6296 6577

3.3 *Tysabri Prescribing Programme Overview*

Figure 5 below provides an overall summary of the Tysabri Prescribing Programme



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5 Appendices

Appendix 1. Package Insert (PI)

Appendix 2. Patient Information Leaflet (PIL)

Appendix 3. Patient Alert Card

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

Appendix 5. Letter of undertaking

Appendix 6. Pre-Infusion Questionnaires

Appendix 7. PML Data Collection Forms (Suspect, Month 3, 6, 12, and 24).