Physician* Information and Management Guidelines for Patients With Multiple Sclerosis Receiving TYSABRI™ (Natalizumab) (IV & SC) Therapy

Version 22: November 2023

***TYSABRI™ therapy is to be initiated and supervised by specialised physicians experienced in the diagnosis and treatment of neurological conditions**

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1. INTRODUCTION

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

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

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

It is recommended that physicians initiating and supervising treatment with TYSABRI should share Appendix 5 of this document with healthcare professionals (HCPs) who are involved in the administration of TYSABRI SC outside a clinical setting (OCS). Appendix 5 includes the OCS Administration Checklist which must be completed by the administering HCP for each patient, prior to each administration. An informational supplement on PML risk factors, monitoring, and diagnosis, is also included to allow for better understanding and usability of the Checklist by HCPs. As the educational needs of different HCPs may vary, additional sections of the PID may be reviewed by local HCPs at their discretion.]

The guidance document focuses primarily on PML, which currently remains the most important adverse reaction affecting patients treated with TYSABRI.

2. PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY

Physicians initiating and supervising treatment with TYSABRI, radiologists who are involved in the differential diagnosis of PML, and HCPs involved in the administration of TYSABRI should be aware that opportunistic infections, including PML, may occur during TYSABRI therapy. An opportunistic infection is an infection due to an organism that generally does not cause disease or that causes only mild or self-limited disease, for example, oesophageal candidiasis, mycobacterial infections, and disseminated viral infections. Opportunistic infections occur in people with weakened immune systems. Cases of PML have been reported in patients during TYSABRI treatment and up to 6 months after the last dose of TYSABRI. Patients and their caregivers need to be advised of symptoms that may be indicative of early PML and continue to be vigilant through the treatment duration and 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. Aetiology and Epidemiology

PML is a subacute, evolving infectious disease of the CNS caused by John Cunningham virus (JCV). Cases have also been reported as a consequence of immunosuppressant (IS) treatment of patients with autoimmune disorders and solid organ transplant recipients.

PML affects the subcortical white matter and is caused by the reactivation of JCV, a human polyomavirus [Wollebo 2015]. Initial infection with JCV is thought to occur during 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, reactivation of this neurotropic virus can occur, resulting in PML.

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 (EU) 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 [Bozic 2014]. In general, anti-JCV antibody prevalence did not appear to be affected by known risk factors such as prior IS use, prior exposure to TYSABRI, or duration of TYSABRI exposure.

2.2. 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. PML in TYSABRI-Treated Patients

PML is an uncommon but serious infection that has been associated with the use of TYSABRI. During extended premarketing authorisation 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]. Patients with confirmed PML in the postmarketing setting are followed up for up to 24 months following diagnosis. Of the 873 TYSABRI-treated patients with confirmed PML through 07 August 2021, the survival rate was 76% (662 patients are alive), and the mortality rate was 24% (211 patients died).

Two general mechanisms have been suggested to explain the association between natalizumab treatment and PML. The first is that blocking α4 integrin decreases lymphocyte trafficking, and the subsequent reduction in immune surveillance allows for the activation of a latent infection in the nervous system. The second suggested mechanism is associated with the finding that deletion of α4 integrin is associated with increased numbers of B cells and immature progenitor cells released from the bone marrow. Both of these cell populations may be reservoirs of latent JCV [Chalkias 2014; Frohman 2014; Monaco 1996; Warnke 2011].

2.4. PML Risk Factors

All data available to characterise PML risk are from the IV route of administration. Considering the similar PD profiles, the same PML risk and relevant risk factors are assumed for the different routes of administration. 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.** Infection with JCV results in the production of anti-JCV antibodies that are detectable in the 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 (STRATIFY JCV™ DXSELECT™) 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.

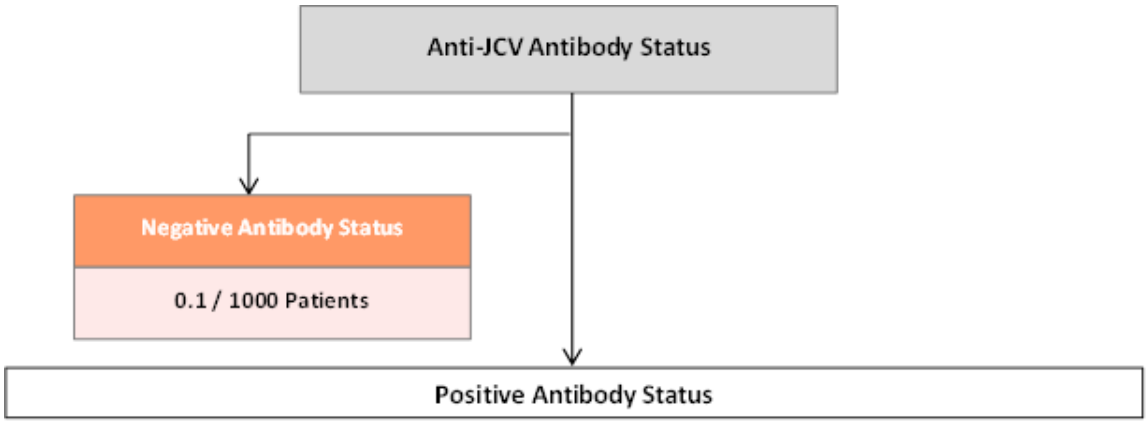
Patients who have all 3 risk factors for PML (i.e., are anti-JCV antibody positive, have received more than 2 years of TYSABRI therapy, and have received prior IS therapy) have a higher risk of PML. In anti-JCV antibody-positive, TYSABRI-treated patients who have not used prior IS therapies, the level 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 less than or equal to 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 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 following year in patients treated with TYSABRI for 24 months. The individual treatment length of each patient takes drop-outs into account (e.g., treatment discontinuation). 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 prior use of these 5 IS therapies lead to an increased PML risk during TYSABRI treatment 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. Further stratification of PML risk by anti-JCV antibody index interval for patients with no prior use of IS was derived from combining the overall yearly risk with the antibody index distribution.

Figure 1: PML Risk Estimates Algorithm

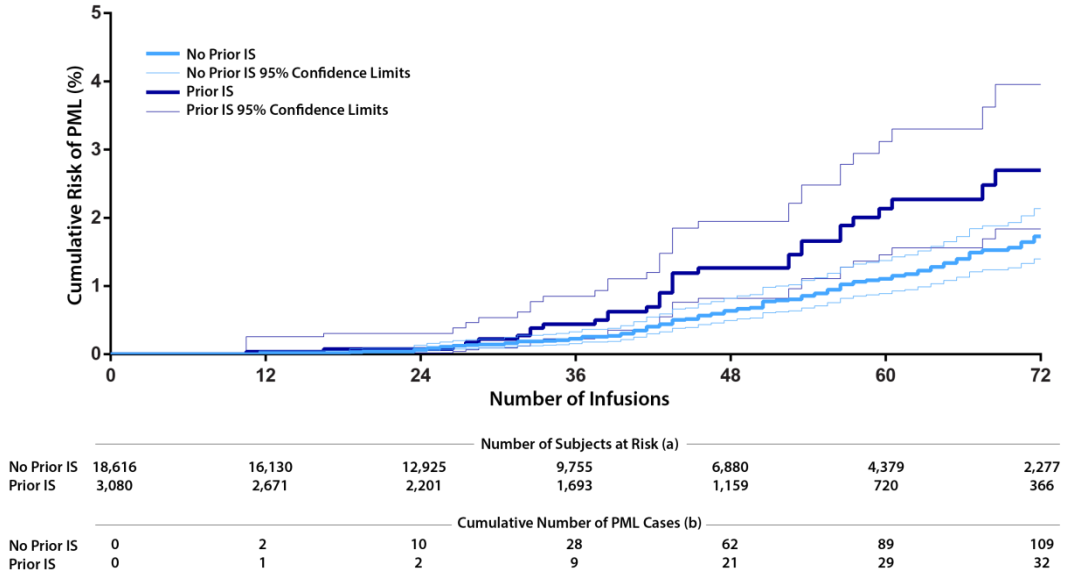


Natalizumab Exposure	PML risk estimates per 1000 patients				
	Patients without prior IS use				Patients with Prior IS use
	No index value	Antibody Index ≤ 0.9	Antibody Index > 0.9 ≤ 1.5	Antibody Index > 1.5	
1-12 months	0.1	0.1	0.1	0.2	0.3
13-24 months	0.6	0.1	0.3	0.9	0.4
25-36 months	2	0.2	0.8	3	4
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.
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 takes into account the individual treatment length of each patient with consideration of drop-outs (e.g., treatment discontinuation).

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

2.5. Extending the Dosing Interval for PML Risk Mitigation

It should be noted that the standard interval dosing (SID) for TYSABRI is 300 mg administered once every 4 weeks (Q4W).

The analysis of US anti-JCV antibody-positive TYSABRI patients (TOUCH prescribing program) supports that there is a significant reduction in the risk of associated PML in anti-JCV antibody-positive patients treated with an average TYSABRI dosing interval of approximately 6 weeks (Q6W), so-called extended interval dosing (EID), compared with the approved dosing regimen, which is every 4 weeks (refer to the SmPC Section 5.1 [Pharmacodynamic effects]). In accordance with SmPC Section 4.4 (Special warnings and precautions for use) if utilising extended interval dosing, caution is required because the efficacy of extended interval dosing has not been established and the associated benefit/risk balance is unknown.

The Study 101MS329 (NOVA, EudraCT Number: 2018-002145-11), Part 1 showed that the safety profile of TYSABRI 300 mg IV once in 6 weeks group was similar to that of TYSABRI 300 mg IV once in 4 weeks group. No new safety findings were

identified during this study, recognizing that this study was not designed to be informative on rare events such as PML. Of note, there was one event of asymptomatic PML reported in the Q6W group. This one case had additional known risk factors (anti-JCV antibody index >1.5 and > 2 years of TYSABRI treatment) [Foley 2022].]

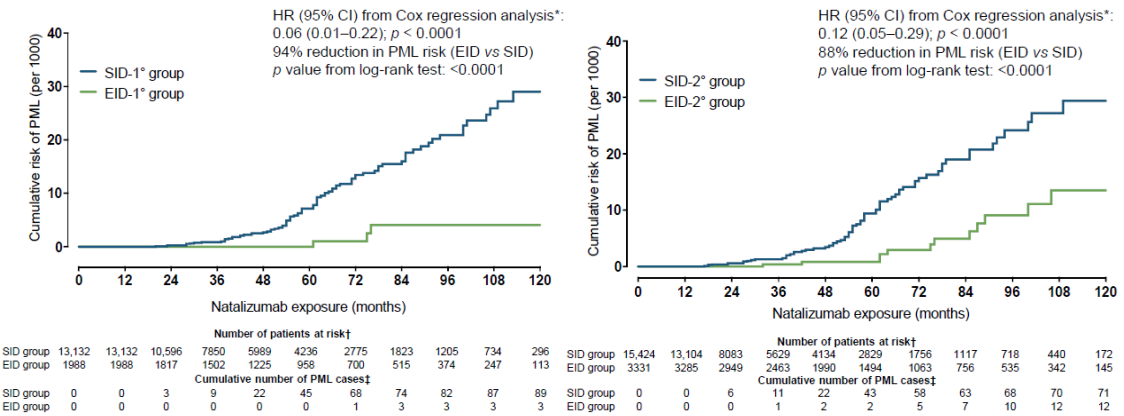
All information available to date on EID efficacy and safety come from evaluation of the IV route of administration. There are no data available on either the safety or efficacy of EID with SC route of administration and thus neither the benefits nor risks of EID SC has been established.

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 (US) was conducted to compare the risk of PML between patients who received SID and those who received EID. Three distinct analyses of EID versus standard interval dosing were performed. Each analysis represented a different real-world clinical practice scenario of extending the interval between doses. The analyses used different inclusion criteria (definitions) for patients on EID based on the number of doses received during specified time periods to test different hypotheses about the potential effect of EID on PML risk [Ryerson 2019]. EID 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. Analyses showed that the majority of EID patients had received SID during the first 18 months of TYSABRI exposure. In the last 18 months of TYSABRI treatment the median number of doses received by EID patients was 13 or approximately one dose every 42 days (6 weeks). The secondary definition identified EID periods of ≥ 6 months occurring at any time during the treatment history with the majority of patients included having switched to EID after > 1 year of the SID (median 25 infusions). KM estimates of time to PML and the probability of developing PML for EID versus SID are presented in Figure 3. The analyses concluded that EID treatment after a period of SID treatment is associated with a lower risk of PML than SID treatment in anti-JCV antibody-positive patients. Efficacy data were not available within this dataset, preventing any conclusions on EID benefit/risk. Even though the risk of PML in EID patients may be lower according to this analysis, patients treated with EID should receive monitoring for PML following the same guidance as that provided for patients treated in accordance with SID.

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

Efficacy has been modelled for patients who switch to longer dosing after ≥1 year of approved dosing with this medicinal product under intravenous administration and who did not experience a relapse in the year prior to switching. Current pharmacokinetic/pharmacodynamic statistical modelling and simulation indicate that the risk of MS disease activity for patients switching to longer dosing intervals may be higher for patients with dosing intervals ≥7 weeks. No prospective clinical studies have been completed to validate these findings.]

2.6. Recommended Patient Monitoring

2.6.1. 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 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 every 6 months is recommended. Retesting low index patients who have no history of prior IS use every 6 months once they reach 2 years of treatment point is recommended to inform on appropriate patient MRI monitoring.

In the STRATIFY-1 clinical study, approximately 11% of patients changed serostatus from anti-JCV antibody negative to positive each year. Approximately 12-16% change serostatus from antibody negative to positive in the second-generation assay reported in Unilabs real world data over a median duration of 12 months. In the STRATIFY-2

clinical study, approximately 6% of patients changed serostatus from anti-JCV antibody positive to negative each year.

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. The use of plasmapheresis/plasma exchange (PLEX) or intravenous immunoglobulin (IVIg) can affect meaningful interpretation of serum anti-JCV antibody testing. Patients should not be tested for anti-JCV antibodies within 2 weeks of PLEX due to removal of antibodies from the serum, or within 6 months of IVIg treatment (i.e., 6 months = 5× half-life for immunoglobulins).

2.6.2. Recommended MRI Monitoring for Early Detection of PML

In 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:

1. 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.
2. 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)

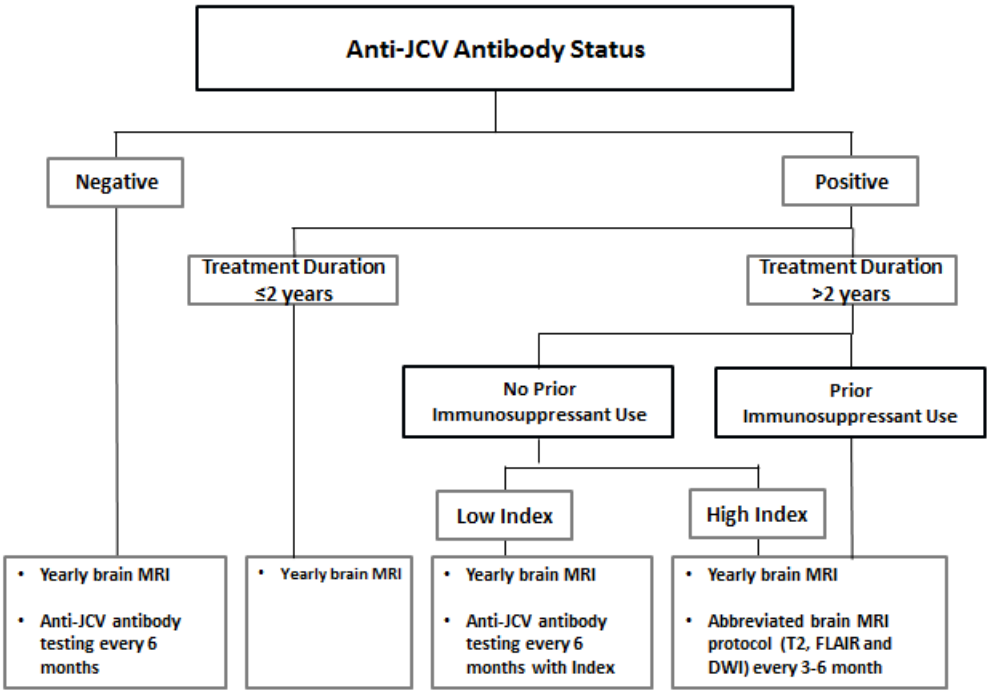
     or

   - 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.
3. MRI should be performed at the first sign of any symptoms indicative of the possibility of PML.

Current evidence suggests that the risk of PML is low at an index less than or equal to 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 information into consideration; 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**[1]	Abbreviated MRI **Protocol**[2]
• 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

[1] Baseline and routine annual scans for all patients.
[2] Safety monitoring in high-risk patients.
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.
*The use of gadolinium-based contrast agents is not recommended for PML screening. The use of gadolinium-based contrast agents is recommended to further assess lesions that are suspicious for PML on standard monitoring or screening MRI, to monitor PML, and to detect and monitor PML-immune reconstitution inflammatory syndrome [Wattjes 2021].

If MRI lesions suggestive of 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.

2.7. Diagnosis of PML

The consensus statement on PML diagnostic criteria published by the American Academy of Neurology requires clinical, radiographic, and virologic findings or typical histopathological findings and the presence of JCV [Berger 2013]. These 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 2014] (see Section 2.7.4).

In Cases of PML, these may be reported using the Medicines Authority ADR reporting form, which is available online at http://www.medicinesauthority.gov.mt/adrportal, and sent by post or email to;
P: Pharmacovigilance Section at Post-Licensing Directorate, Medicines Authority, Sir Temi Żammit Buildings, Malta Life Sciences Park, San Ġwann SĠN 3000
E: postlicensing.medicinesauthority@gov.mt

Or to the local agent on behalf of the MAH:
All reports can be sent to pharmacovigilance@pharmamt.com or by post to:
103, Stuart Street,

Gzira, GZR 1054

2.7.1. Important Considerations

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 receive counselling on the need to be vigilant for these symptoms while the patient is receiving TYSABRI therapy and 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 2.5). TYSABRI dosing should only be restarted when the diagnosis of PML is confidently excluded (if necessary, by repeating clinical, MRI, and laboratory investigations if suspicion of PML remains).

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

TYSABRI should be permanently discontinued if PML is confirmed.

2.7.2. Clinical Assessment

Any new or recurrent neurological symptoms should require prompt and careful evaluation in order to ascertain the underlying pathology. In a patient whose MS disease activity has been stable on TYSABRI, 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 on MRI should be carefully evaluated, particularly when an abbreviated protocol has been performed (see Section 2.7.3). Table 2 highlights the clinical features that may help differentiate MS lesions from PML. It should be noted that the table is not all inclusive and that symptomatic overlap between symptoms of these conditions exists. **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 of PML.** The history and pattern of previous and current symptoms and signs are important to note and will facilitate the management of 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 • Marked weaknesses • Hemiparesis • Sensory deficits • Vertigo • 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. Some overlap of clinical features of MS and PML may occur.
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.

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. TYSABRI therapy should be suspended if JCV GCN and/or PML is suspected and permanently discontinued if a diagnosis of JCV GCN and/or PML is confirmed.

2.7.3. MRI Differentiation Between PML and MS Relapse

A full MRI protocol (Table 1) is recommended for the follow-up of patients receiving TYSABRI, to obtain the best possible images to assist with clinical decision making [Wattjes 2021].

The use of gadolinium-based contrast agents is not recommended for PML screening. The use of gadolinium-based contrast agents is recommended to further assess lesions that are suspicious for PML on standard monitoring or screening MRI, to monitor PML, and to detect and monitor PML-immune reconstitution inflammatory syndrome [Wattjes 2021].

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 [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).

In Cases of PML, these may be reported using the Medicines Authority ADR reporting form, which is available online at http://www.medicinesauthority.gov.mt/adrportal, and sent by post or email to;
P: Pharmacovigilance Section at Post-Licensing Directorate, Medicines Authority, Sir Temi Żammit Buildings, Malta Life Sciences Park, San Ġwann SĠN 3000
E: postlicensing.medicinesauthority@gov.mt

Or to the local agent on behalf of the MAH:
All reports can be sent to pharmacovigilance@pharmamt.com or by post to:
103, Stuart Street,
Gzira, GZR 1054

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.

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

2.7.4. Laboratory Investigation

The detection of JCV DNA by PCR in the CSF confirms the diagnosis of PML in patients with appropriate and associated MRI findings. 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. Biogen is not in a position to certify any laboratory. However, Biogen 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.

Details of the procedure for the collection, handling, and transport of samples to the central facility are available from Medical Affairs in Malta.
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2.8. Management of PML

Immune reconstitution

The data available suggest that early PML recognition is important for an optimal clinical outcome [Clifford 2015; Kappos 2019].

PLEX and/or immunoadsorption (IA) has been reported for rapid removal of TYSABRI from the body with the intention of accelerated restoration of CNS immunosurveillance. However, based on a retrospective analysis of TYSABRI-treated patients, no difference was observed on 2-year survival after PML diagnosis between patients who received PLEX and those who did not [Kappos 2019]. Physicians should use medical judgement when considering the use of PLEX to treat PML. And, if PLEX is used, patients should be closely monitored for the development of IRIS (see Section 2.8.1), which occurs in almost all patients treated with PLEX and appears to occur more rapidly than in patients who are not treated with PLEX [Carruthers and Berger 2014; Clifford 2010].

Antivirals and other adjuvants

To date, no clinical trial has demonstrated a beneficial effect of antiviral agents in the management of PML. Real-world reports of PML outcomes associated with use of antivirals, including mefloquine, mirtazapine, and filgrastim, are mixed and inadequate to recommend any treatment approach [Kappos 2019; Williamson and Berger 2017].

2.8.1. Treatment of Immune Reconstitution Inflammatory Syndrome

IRIS occurs in almost all TYSABRI-associated PML patients after withdrawal or removal of the medicinal product. IRIS is thought to result from the restoration of immune function in patients with PML, which can lead to serious neurological complications and may be fatal. Monitoring for development of IRIS and appropriate treatment of the associated inflammation during recovery from PML should be undertaken.

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.

It may become necessary to treat the active immune reaction to prevent potential damage caused by IRIS [Elston and Thaker 2009], but it 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 [Clifford 2015]. The following steroid regimens have been reported for the treatment of IRIS in the literature:

1. Oral prednisone 1.5 mg/kg/day for 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 [Williamson and Berger 2017].

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 2017].

2.9. Prognosis of PML

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 2.8.

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. As of 07 August 2021, 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 (54.2% versus 34.0%, respectively). Conversely, 22.9% of asymptomatic patients had widespread PML on MRI compared with 39.9% of symptomatic patients.

As of 07 August 2021, asymptomatic PML patients also had a higher survival rate compared with symptomatic patients (92.4% versus 73.2%, respectively).

2.10. PML Diagnosed After Discontinuation of TYSABRI

PML has been reported after the discontinuation of TYSABRI. Patients and physicians should remain alert for any new signs or symptoms that may be suggestive of PML for approximately 6 months after discontinuation, taking into account the switch to other MS disease-modifying treatments that are associated with a risk of PML.

As of 07 August 2021, a total of 112 confirmed cases of PML have been reported in patients where PML onset (i.e., date of first PML clinical or radiographic symptoms) occurred more than 4 weeks (30 days) after the last TYSABRI infusion. Of the 112 cases where time from last infusion to onset of PML is known, the majority of cases (91/112; 81%) had PML onset within 3 months (90 days) of the last TYSABRI infusion, and 20 (18%) patients had PML onset 4 to 6 months (91 to 180 days) after the last infusion. One patient had PML onset approximately 8 months after the last infusion. In this case, TYSABRI was discontinued due to an anti-JCV antibody index > 1.5, the patient had experienced > 2 years of TYSABRI treatment, and the patient had been switched to another MS disease-modifying treatment associated with a risk of PML (approximately 4 months prior to PML onset).

3. EDUCATIONAL GUIDANCE

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 of treatment 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, and the same monitoring protocol should be continued for approximately 6 months after discontinuation of TYSABRI.

Patients should also be informed of the increased risk of opportunistic infections.

A template Treatment Initiation Form, Treatment Continuation Form, and Treatment Discontinuation Form are provided in Appendix 4.

The Outside a Clinical Setting (OCS) Administration Checklist & accompanying Decision Tree for use by HCPs administering TYSABRI SC outside a clinical setting (e.g., at home) is provided in Appendix 5, along with an informational supplement for administering HCPs.]

In Cases of PML, these may be reported using the Medicines Authority ADR reporting form, which is available online at http://www.medicinesauthority.gov.mt/adrportal, and sent by post or email to;
P: Pharmacovigilance Section at Post-Licensing Directorate, Medicines Authority, Sir Temi Żammit Buildings, Malta Life Sciences Park, San Ġwann SĠN 3000
E: postlicensing.medicinesauthority@gov.mt
Or to the local agent on behalf of the MAH:
All reports can be sent to pharmacovigilance@pharmamt.com or by post to:
103, Stuart Street,

3.1. Informing Patients About Benefits and Risks

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

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

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

In addition, locally agreed templates for a Treatment Initiation Form, a Treatment Continuation Form at 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 forms should be signed, provided to and discussed with patients before initiation of treatment, after patient

counselling at 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.

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 opportunistic infections, including PML (e.g. changes in mood, behavior, memory, motor weakness, speech, or communication difficulties) may occur up to 6 months after discontinuation and patients and their partners and caregivers should report any suspect changes in neurological status during this time.

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

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

3.3. Treatment forms

Treatment forms (see Appendix 4) are included as part of the Physician Pack. Additional forms can be ordered from the local company office; contact details are contained in the pack.

3.4. Outside a Clinical Setting (OCS) Administration Checklist

The OCS Administration Checklist & accompanying Decision Tree (see Appendix 5) are included for use by HCPs administering TYSABRI SC outside a clinical setting (e.g., at home). This educational tool was developed to aid HCPs in identifying patients with signs and symptoms of PML prior to each administration, and to guide escalation to and contact with the specialist physician if PML is suspected. An HCP Informational Supplement on PML risk factors, monitoring, and diagnosis, is also included in Appendix 5 to allow for better understanding and usability of the Checklist by HCPs.

Administration of TYSABRI SC outside a clinical setting does ***not*** replace the need for regular contact with, and clinical monitoring by, the patient's specialist physician. It is the responsibility of the specialist physician to determine the patient's suitability for TYSABRI SC administration outside a clinical setting at regular intervals, and to ensure that appropriate monitoring for PML (including risk factors and magnetic resonance imaging [MRI] screening) outside a clinical setting is maintained, as in the clinical setting, in alignment with the recommendations as noted in the European Union (EU) TYSABRI SC Summary of Product Characteristics (SmPC)

It is recommended that the administering HCP has access to the patient's current medication list in order to complete a Medication Reconciliation in the OCS Administration Checklist at each appointment outside a clinical setting, prior to TYSABRI SC administration.

Additional OCS Administration Checklists can be ordered from the local company office; contact details are contained in the Physician Pack.]

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5. APPENDICES

APPENDIX 1. SUMMARY OF PRODUCT CHARACTERISTICS (SMPC)

APPENDIX 2. PACKAGE LEAFLET (PL)

APPENDIX 3. PATIENT ALERT CARD

APPENDIX 4. TREATMENT INITIATION FORM, TREATMENT CONTINUATION FORM, AND TREATMENT DISCONTINUATION FORM

APPENDIX 5. OUTSIDE A CLINICAL SETTING (OCS) ADMINISTRATION CHECKLIST & HCP INFORMATIONAL SUPPLEMENT