HCP Informational Supplement

This supplement is intended for use by HCPs administering Tysabri SC outside a clinical setting (OCS). It provides relevant background information on Progressive Multifocal Leukoencephalopathy (PML), to allow for better understanding and usability of the OCS Administration Checklist which must be completed for each patient, prior to each administration of Tysabri SC OCS. It is available along with the OCS Administration Checklist as Appendix 5 to the Physician Information and Management Guidelines for Patients With Multiple Sclerosis Receiving TYSABRI Therapy (PID).

PML Risk Factors

All data available to characterise PML risk are from the IV route of administration. Considering the similar pharmacodynamic (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 (IS) therapy**. Patients who have a history of treatment with an IS prior to starting TYSABRI are also at increased risk of developing PML.

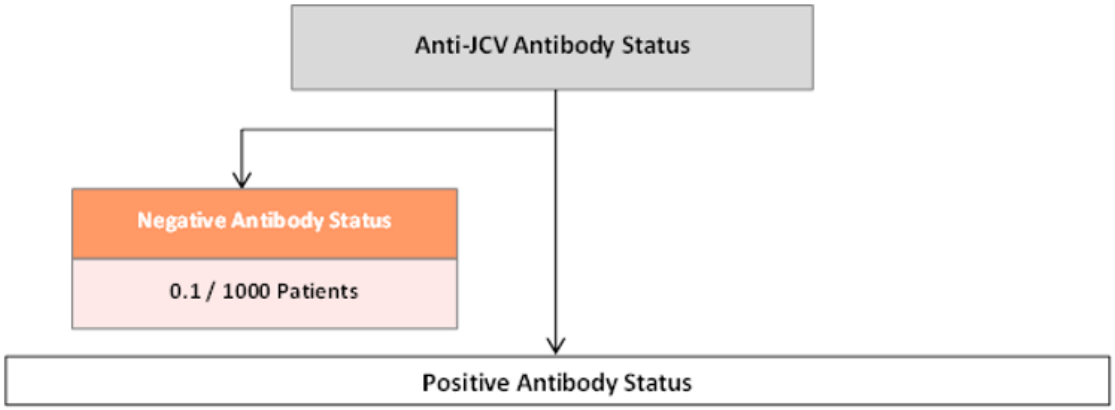
Patients who have all 3 risk factors for PML (i.e., are anti-JCV antibody positive, have received more than 2 years of TYSABRI therapy, and have received prior IS therapy) have a higher risk of PML. In anti-JCV antibody-positive, TYSABRI-treated patients who have not used prior IS therapies, the level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

Recommended Patient Monitoring

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).

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 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 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

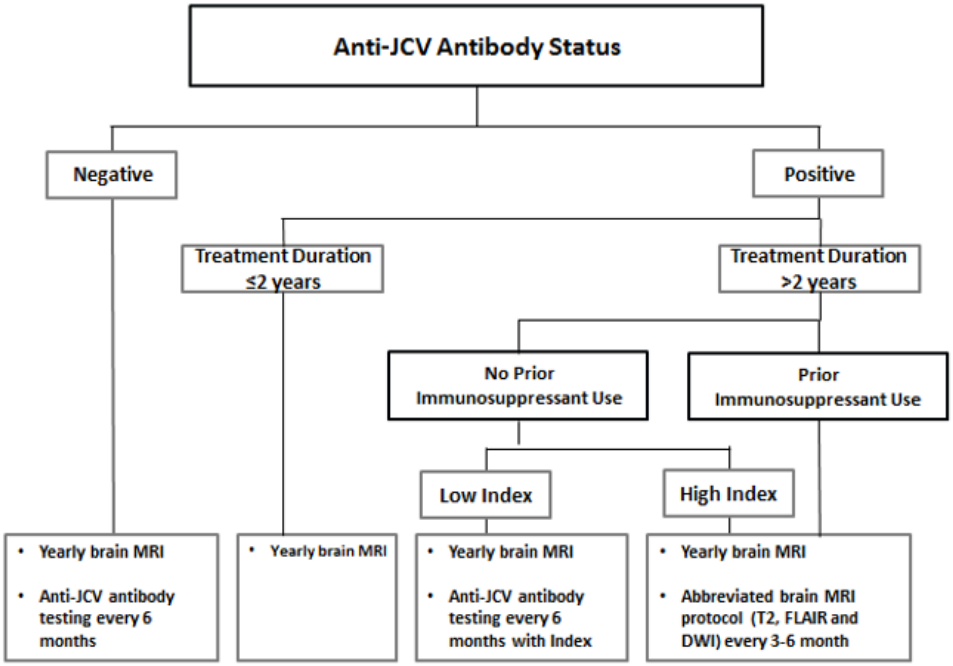
- Patients with a high anti-JCV antibody index who have received more than 2 years of TYSABRI therapy and without prior history of IS therapy.

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 2.

Figure 2: Recommended Patient Monitoring



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

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].

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 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).

As noted on the OCS Administration Checklist, HCPs administering TYSABRI SC outside a clinical setting (e.g., at home) must escalate concerns to the specialist physician if PML is suspected, whereas it is the responsibility of the specialist physician to determine next steps regarding the appropriateness and timing of TYSABRI administration.

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. 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.

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. Table 1 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 and HCPs 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 1: 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 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.

Additional educational information on PML is available in the Physician Information and Management Guidelines for Patients with Multiple Sclerosis receiving TYSABRI therapy (PID), which can be referred to by administering HCPs at their discretion.

Educational Guidance

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 of the PID) 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. As noted on the OCS Administration Checklist ("Reporting of Side Effects"), the administering HCP must ensure that the patient has their Patient Alert Card.

Outside a Clinical Setting (OCS) Administration Checklist

The OCS Administration Checklist & accompanying Decision Tree (see Appendix 5 of the PID) 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.

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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