Tysabri® (natalizumab)	**Adverse drug event reporting channels:** Malta Medicines Authority: https://medicinesauthority.gov.mt/adrportal OR Pharma.mt Ltd (obo Biogen – MAH): pharmacovigilance@pharmamt.com

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"Tysabri (Natalizumab) Healthcare Professional Guide"

Safety information for risk minimisation of Progressive Multifocal Leukoencephalopathy (PML) in Patients with Multiple Sclerosis Receiving TYSABRI™ (Natalizumab) Therapy

Version 1

February 2026

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1. PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY: EPIDEMIOLOGY, AETIOLOGY, AND PATHOLOGY

This document has been developed for healthcare professionals (HCPs) initiating and supervising patient treatment with TYSABRI (Natalizumab). This educational material is part of the educational programme in accordance with the conditions of the Marketing Authorisations of TYSABRI (Natalizumab), in order to ensure its safe and effective use. It contains information to be used in conjunction with the approved prescribing informationand provides additional risk mitigation measures.

The educational programme also includes a patient information pack (Patient Card, TYSABRI (Natalizumab) treatment initiation, continuation and discontinuation forms and, for patients self-administering or caregivers administering Tysabri SC, Pre-administration Checklist).

The objective of this document is to provide guidance to HCPs for the management of patients receiving TYSABRI (Natalizumab) either intravenously (IV) or subcutaneously (SC). It provides relevant background information on the risk for Progressive Multifocal Leukoencephalopathy (PML) associated with the use of TYSABRI (Natalizumab) and provides recommendations on PML risk mitigation and surveillance. It can also be shared by the treating physician with other HCPs peripherally involved in the care and management of these patients (e.g., radiologists)

Progressive multifocal leukoencephalopathy (PML) is an uncommon but serious subacute, evolving infectious disease of the central nervous system (CNS) that is caused by reactivation of John Cunningham virus (JCV), typically in the setting of immunosuppression.

PML affects the subcortical white matter and is caused by the reactivation of JCV, a human polyomavirus (Wollebo et al. 2015). Initial infection with JCV is thought to occur during childhood. A seroprevalence study utilising the serum anti-JCV antibody assay (STRATIFY JCV™) in over 6 000 patients with MS demonstrated the prevalence of anti-JCV antibodies to be approximately 55% (Bozic et al. 2014). The detection of anti JCV antibodies and the JCV antibody index are tools for stratifying MS patients for higher or lower risk of developing PML, they are not diagnostic of PML.

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.

2. PML RISK FACTORS

All data available to characterise PML risk for patients on TYSABRI (Natalizumab) therapy are from the IV route of administration. Considering the similar pharmacodynamic (PD) profiles, the risk of PML and risk factors for PML are assumed to be the same for the different routes of administration and administration settings. The following risk factors have been associated with the development of PML during TYSABRI (Natalizumab) 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 used in combination with the other identified risk factors described below.
- **Treatment duration**. The risk of PML increases with TYSABRI (Natalizumab) therapy duration, especially beyond 2 years.
- **Prior IS therapy**. Patients who have a history of IS treatment prior to starting TYSABRI (Natalizumab) 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 (Natalizumab) therapy, and have received prior IS therapy) have a higher risk of PML. In patients who have been receiving treatment with TYSABRI (Natalizumab) for longer than 2 years and who have not used prior IS therapies, the level of anti-JCV antibody response using STRATIFY JCV™ DXSELECT™ (index) is associated with the level of risk for PML: the risk of PML is low at an index less than or equal to 0.9 and increases substantially at an index above 1.5 (Ho et al. 2017) .

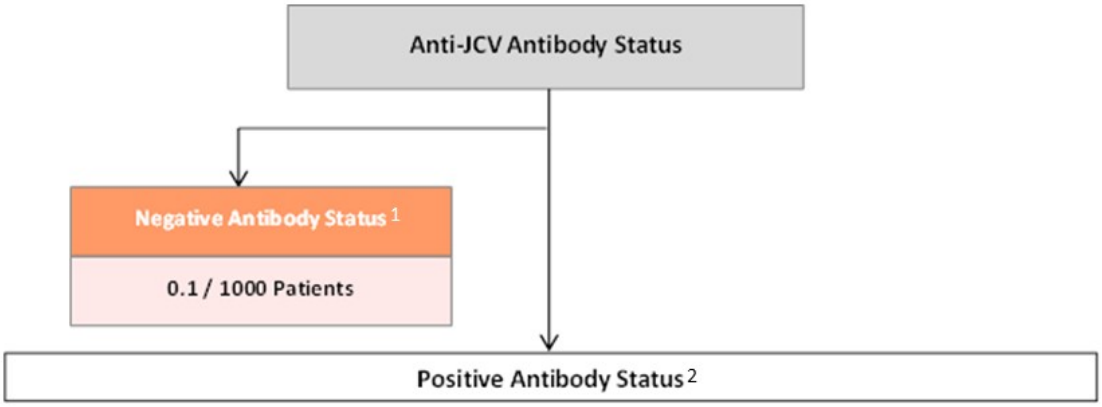
In anti-JCV antibody positive patients, extended interval dosing (EID) of TYSABRI (Natalizumab) (average dosing interval of approximately 6 weeks via IV route administration) is suggested to be associated with a lower PML risk compared to approved dosing of every 4 weeks (standard interval dosing, SID). However, the efficacy of extended interval dosing is not established. No clinical data are available on either the safety or efficacy of dosing every 6 weeks with TYSABRI (Natalizumab) SC route of administration.

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

PML has been reported after the discontinuation of TYSABRI (Natalizumab) 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.

The PML Risk Estimates Algorithm (Figure 1) summarises PML risk by anti-JCV antibody status, prior IS use, and duration of TYSABRI (Natalizumab) therapy (by year of treatment) and stratifies this risk by index value when applicable. This algorithm was created based on data derived from TYSABRI (Natalizumab) treated patients tested using the specifically designed STRATIFY JCV DXSELECT™ test (Ho et al. 2017).

Figure 1: PML Risk Estimates Algorithm



Natalizumab Exposure[3]	PML risk estimates per 1000 patients				
	Patients without prior IS use				Patients with prior IS use[4]
	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

Abbreviations: IS = immunosuppressant; JCV = John Cunningham virus; PML = progressive multifocal leukoencephalopathy.
[1]Risk estimate is based on data from approximately 125,000 TYSABRI-exposed patients.
[2]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 (Natalizumab) exposure period is the PML risk estimated for the following year in patients treated with TYSABRI (Natalizumab) for 24 months. 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.
[3]Exposure is shown up to 72 months only as data beyond 6 years of treatment are scarce.
[4]Risk estimates are based on TYSABRI (Natalizumab) clinical trial data where prior IS use included mitoxantrone, methotrexate, azathioprine, cyclophosphamide, and mycophenolate mofetil.

3. RECOMMENDED PATIENT MONITORING

3.1. Testing for Anti-JCV Antibodies

Testing serum for anti-JCV antibodies provides supportive information for risk stratification of PML with TYSABRI (Natalizumab) therapy. Testing for serum anti-JCV antibodies is recommended prior to initiating TYSABRI (Natalizumab) therapy. Due to the possibility of seroconversion, retesting for anti-JCV antibodies every 6 months is recommended in anti-JCV antibody-negative patients and in patients with a low anti-JCV antibody index with no history of prior IS use once they reach 2 years of treatment (Figure 2).

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

The anti-JCV antibody assay should not be used to diagnose PML. 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 (due to exogenous antibodies) as these procedures can impact the meaningful interpretation of the testing.

3.2. Recommended MRI Monitoring for Early Detection of PML

In patients who develop new neurological symptoms or signs once on TYSABRI (Natalizumab)therapy, MRI may assist in differentiating PML lesions from MS plaques. In high-risk asymptomatic patients, frequent MRI surveillance may lead to an earlier diagnosis of PML and better clinical outcomes (Prosperini et al. 2016; Scarpazza et al. 2020; Wattjes et al. 2015). Recommendations for MRI monitoring are summarised below:

1. Before initiation of treatment with TYSABRI (Natalizumab), a recent (usually within 3 months) full MRI should be available as a reference. While on TYSABRI (Natalizumab) therapy and for 6 months after discontinuation of therapy, a full MRI should be repeated at least annually. Physicians should evaluate the annual full MRI for any signs of PML.
2. More frequent MRIs (e.g., on a 3- to 6-month 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 (Natalizumab)therapy **and** have received prior IS therapy)

     or

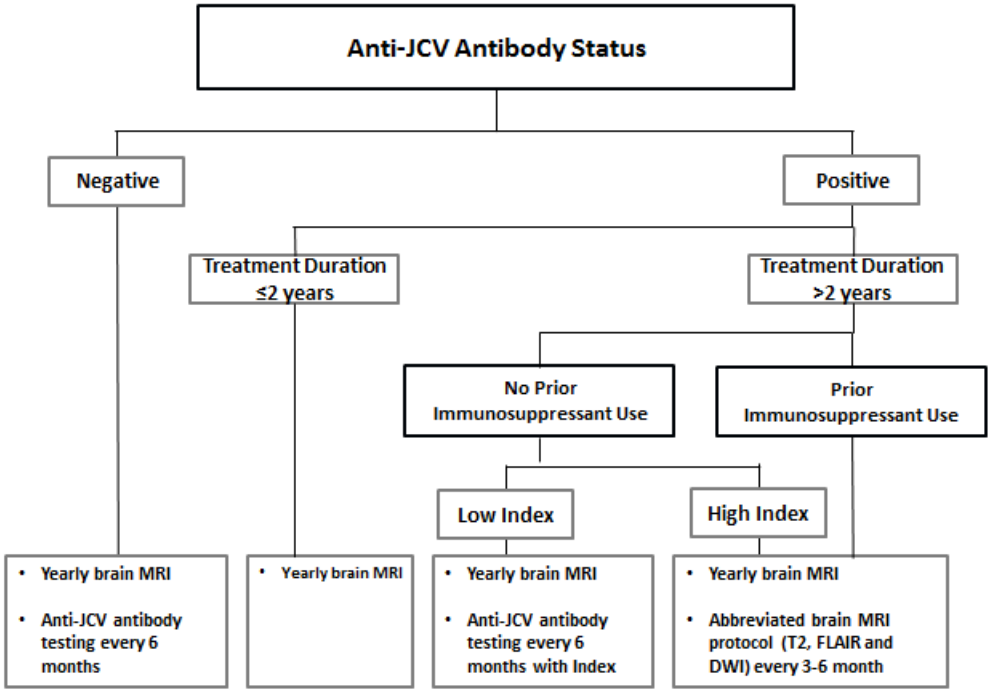
   - Patients with a high anti-JCV antibody index (>1.5) who have received more than 2 years of TYSABRI (Natalizumab)therapy without prior IS therapy.
3. MRI should be performed at the first sign of any symptoms indicative of the possibility of PML.

For patients with an anti-JCV antibody index between 0.9 and 1.5, the frequency of MRI surveillance is at the discretion of the treating physician.

As an overview, full MRI protocol includes FLAIR (fluid-attenuated inversion recovery, which has the highest sensitivity), T2-weighted, diffusion-weighted imaging (depiction of active and acute PML lesions) and T1-weighted pre- and post-contrast sequences. Abbreviated protocol should include FLAIR, T2-weighted and diffusion-weighted imaging sequences (Wattjes et al. 2015).

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.
Low index = anti-JCV antibody ≤ 0.9
High index = anti-JCV antibody > 1.5

4. DIAGNOSIS OF PML

The diagnosis of PML requires neuropathologic demonstration of the typical histopathologic findings with the techniques to show the presence of JC virus or the presence of clinical and imaging manifestations consistent with the diagnosis and not better explained by other disorders coupled with the demonstration of JC virus by PCR in CSF (Berger et al. 2013). Further, in some situations, PML can be considered confirmed based on MRI findings and detection of JCV DNA alone, without the presence of clinical symptoms (Dong-Si et al. 2014).

INSERT: That the National Competent Authority should be informed about any cases of PML and insert information about any registry or other monitoring system set up in the Member State, including details of how to enter patients.

4.1. Important Considerations

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

In all cases where further investigation of change in neurological status or change in brain MRI is indicated, TYSABRI (Natalizumab) must be suspended and not restarted until non-MS pathology has been confidently excluded. TYSABRI (Natalizumab) 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).

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.

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 (Natalizumab) therapy and for approximately 6 months after the last dose of Tysabri (Natalizumab).

4.2. Clinical Assessment

Any new or recurrent neurological symptoms require prompt and careful evaluation to ascertain the underlying etiology. In a patient whose MS disease activity has been stable on TYSABRI (Natalizumab), such changes warrant an evaluation for 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.

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. In general, MS relapses present with acute (evolving over hours or days) focal neurological symptoms (e.g., diplopia, paraesthesia, paraparesis) that normally stabilize, often improve with corticosteroids, or resolve spontaneously even without therapy. In contrast, PML has a subacute onset and manifests with insidious, progressive symptoms over weeks (e.g., cognitive impairment, behavioural changes, aphasia, marked weakness, hemiparesis).

4.3. MRI Assessment

MRI is recommended for the follow-up of patients receiving TYSABRI (Natalizumab) to obtain the best possible images to assist with clinical decision making.

In both high- and low-risk asymptomatic patients, any new suspicious lesions on MRI should be carefully evaluated, particularly when an abbreviated protocol has been performed.

Fluid-attenuated inversion recovery (FLAIR) is the most sensitive sequence for detection of PML (Wattjes et al. 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 and Barkhof 2014). The use of gadolinium-based contrast agents is recommended to further assess lesions that are suspicious for PML on standard monitoring or **s**creening MRI, to monitor PML, and to detect and monitor PML-immune reconstitution inflammatory syndrome. The use of gadolinium-based contrast agents is not recommended for PML screening.

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.

The following table shows features on MRI 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 et al. 2011; Wattjes and Barkhof 2014; Yousry et al. 2012)

INSERT: Details (if available) of the educational website designed to provide further insight into differentiating PML from MS (this will be added Member State by Member State).

4.4. Laboratory Investigation

The detection of JCV DNA by PCR in the CSF confirms the diagnosis of PML in patients with consistent MRI findings. However, a negative JCV PCR result does not exclude a possible diagnosis of PML, particularly because small volume lesions are associated with lower viral copy numbers (Wijburg et al. 2018). 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.

Quantitative real-time PCR assays should be used to detect JCV DNA to maximise sensitivity and specificity. The PCR assay should have a level of detection of at least 11 copies/mL, since PML has been confirmed in the setting of low copy numbers in the CSF.

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.

5. MANAGEMENT OF PML

There is no specific treatment for PML outside of reducing immunosuppression and restoring the host immune response.

5.1. TYSABRI therapy discontinuation

In all cases where further investigation of change in neurological status or change in brain MRI is indicated, TYSABRI (Natalizumab) must be suspended and not restarted until non-MS pathology has been confidently excluded. TYSABRI (Natalizumab)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).

TYSABRI (Natalizumab)should be permanently discontinued if PML is confirmed.

5.2. Immune reconstitution

PLEX and/or immunoadsorption (IA) have been used for rapid removal of TYSABRI (Natalizumab)from the body with the intention of accelerating restoration of CNS immunosurveillance. Physicians should use medical judgement when considering the use of PLEX to treat PML. If PLEX is used, patients should be closely monitored for the development of Immune Reconstitution Inflammatory Syndrome (IRIS), 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 et al. 2010).

5.3. Antivirals and other adjuvants

To date, no clinical trial has demonstrated a beneficial effect of antiviral agents in the management of PML.

5.4. Immune Reconstitution Inflammatory Syndrome (IRIS)

IRIS occurs in almost all TYSABRI (Natalizumab)-associated PML patients after withdrawal or removal of the medicinal product. IRIS is thought to result from the restoration of immune function. IRIS is generally suspected when patients with PML exhibit signs of clinical worsening as a result of a local inflammatory reaction accompanied by gadolinium enhancement of PML lesions with or without mass effect on brain MRI. Severe sequelae can occur including coma and death. Monitoring for development of IRIS and appropriate treatment of the associated inflammation during recovery from PML should be undertaken. Although it may become necessary to treat the active immune reaction to prevent potential damage caused by IRIS, the diagnosis and management of IRIS is a controversial issue and there is no consensus concerning its treatment. Corticosteroids may be useful to treat IRIS, particularly in patients with severe to life-threatening IRIS (Clifford 2015) . A steroid regimen including intravenous methylprednisolone (1 g/d for 3 or 5 days) with oral taper over 2 months (Williamson and Berger 2017) has been reported for the treatment of IRIS in the literature.

5.5. Prognosis of PML

Improved survival from PML after TYSABRI (Natalizumab)therapy has been associated with a younger age at PML diagnosis, less functional disability before PML diagnosis, a lower JCV viral load at PML diagnosis, and more localised brain involvement on MRI at diagnosis (Dong-Si et al. 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 et al. 2014; Prosperini et al. 2016)

6. FURTHER INFORMATION

HCPs need to discuss the benefit-risk profile of TYSABRI (Natalizumab)treatment with the patient and ensure to provide the patient information pack for TYSABRI (Natalizumab) (Patient Card, TYSABRI (Natalizumab) treatment initiation, continuation and discontinuation forms and, for patients self-administering or caregivers administering TYSABRI (Natalizumab) SC, Pre-administration Checklist). Due to the increased risk of developing PML with increasing treatment duration, the benefits and risks of TYSABRI (Natalizumab) therapy should be individually reconsidered by the specialist physician and the patient or caregivers during the course of therapy. The patient should be reinformed about the risks of PML with TYSABRI (Natalizumab) after 24 months of treatment and should be instructed together with their caregivers on early signs and symptoms of PML. Patients who are discontinuing TYSABRI (Natalizumab) therapy should also be informed that cases of PML have occurred in patients up to 6 months after the last dose of TYSABRI (Natalizumab), and the same monitoring protocol should be continued for approximately 6 months after discontinuation of TYSABRI (Natalizumab).

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

All HCPs should be aware that it is the responsibility of the treating specialised physician to determine the patient's suitability for TYSABRI (Natalizumab) SC administration Outside a Clinical Setting (OCS) either by HCP, the patient themselves or caregiver.

The administration of TYSABRI (Natalizumab) SC OCS and patients self-administering or caregivers administering does not replace the need for regular contact with and clinical monitoring by the patient's treating specialised physician.

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