TYSABRI
(natalizumab)

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 Pre-administration Checklist which must be reviewed for each patient, prior to each administration of TYSABRI SC OCS. It is available along with the Pre-administration Checklist as Appendix 3 to the Physician Information and Management Guidelines for Patients With Multiple Sclerosis Receiving TYSABRI Therapy (PID) and as agreed upon with HPRA.

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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.

PML RISK FACTORS

An important identified risk associated with TYSABRI treatment is Progressive Multifocal Leukoencephalopathy (PML), an uncommon brain infection which can lead to serious neurological complications and may be fatal. It is important that the patient is assessed for signs and symptoms of PML prior to administration of TYSABRI. Cases of asymptomatic PML have been reported that were initially suspected based on MRI findings and later confirmed by positive JCV DNA in the cerebrospinal fluid (CSF). PML has also been reported after the discontinuation of TYSABRI. Patients (including partners and caregivers) 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 following risk factors have been associated with the development of PML during TYSABRI therapy:

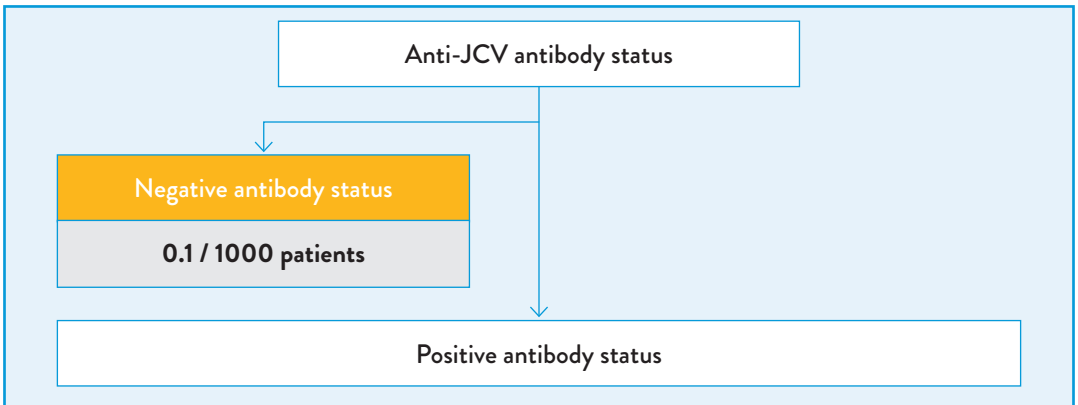
- **The presence of anti-JCV antibodies in blood or serum.** Infection with JCV results in the production of anti-JCV antibodies that are detectable in the blood or serum. Patients who are anti-JCV antibody positive are at an increased risk of developing PML compared with patients who are anti-JCV antibody 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. 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.

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.

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

It is the responsibility of the specialist physician 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.

DIAGNOSIS OF PML

It is the responsibility of the specialist physician to ensure 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

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. 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 SC OCS develop, appropriate referral should be made by the HCP to the specialist physician as PML should always be considered.**

The Pre-administration Checklist (see Appendix 3 of the PID) are included for use by HCPs administering TYSABRI SC OCS. As noted on the Pre-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 prior to each administration. 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, to be initiated by the specialist physician, of change in neurological status or change in brain MRI is indicated, TYSABRI must be suspended by the specialist physician 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 by the specialist physician 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 by the specialist physician 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. HCPs administering TYSABRI SC OCS must escalate concerns of PML to the specialist physician if PML is suspected. 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 by the HCP administering TYSABRI OCS or by the specialist physician further investigations, including MRI evaluation and lumbar puncture and CSF evaluation, should be undertaken as soon as possible by the specialist physician. TYSABRI dosing should be suspended by the specialist physician 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 administering HCP must ensure that the patient has their Patient Alert Card.

The Patient Alert Card must be issued to patients to fill out and carry with them. This card is issued to ensure that patients are aware of the symptoms of PML and where to report these symptoms.

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, behaviour, 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.

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).

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 1 of the PID) are included as part of the Physician Pack. Additional copies of all materials (HCP informational Supplement, Pre-administration Checklist, Treatment Initiation, Continuation and Discontinuation Forms and Patient Alert Cards) can be ordered from MedInfoUKI@biogen.com or by phone 1800 812 719 or can be downloaded from www.medicines.ie

HCPs should refer to the SmPC and PL and these are available via www.medicines.ie

REPORTING OF SIDE EFFECTS

- HCP must report all adverse events to the specialist physician for evaluation, and any suspected adverse reactions via HPRA Pharmacovigilance, website www.hpra.ie
- HCP must ensure that the patient has their Patient Alert Card, and must inform the patient and/or caregiver of the following:
  - If the patient gets any side-effects, talk to your neurologist.
  - This includes any possible side-effects not listed in the Package Leaflet.
  - Side-effects can also be reported directly at www.hpra.ie

PRE-ADMINISTRATION CHECKLIST

The Pre-administration Checklist (see Appendix 3 of the PID) is included for use by HCPs administering TYSABRI SC outside a clinical setting (e.g., at home) or for patients and caregivers administering. This educational tool is intended to aid HCPs and patients and caregivers to identify 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 TYSABRI SC Summary of Product Characteristics (SmPC).

The Pre-administration Checklist should be read in conjunction with the TYSABRI SC SmPC and Package Leaflet (PL) and is not intended as replacements for these documents. Please refer to the TYSABRI SC SmPC and the PL for further information about the approved use of TYSABRI, available at www.medicines.ie

Additional Pre-administration Checklists can be ordered from MedInfoUKI@biogen.com or by phone on 1800 812 719 or can be downloaded from www.medicines.ie

The administering HCP must ensure that the patient has their Patient Alert Card.

REFERENCES

- Berger JR, Aksamit AJ, Clifford DB, et al. PML diagnostic criteria: consensus statement from the AAN Neuroinfectious Disease Section. Neurology. 2013;80(15):1430-8.
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