Medical Information
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TYSABRI® (natalizumab): PML Incidence in Patients Receiving TYSABRI

This information is provided as an educational resource for healthcare providers in response to an unsolicited request and should be considered current as of the date listed herein. It is not intended to be a substitute for consultation and review of reference materials and medical literature pertaining to individual clinical circumstances. Healthcare providers should make all treatment decisions based on the context of the situation and their clinical judgment.

Overview

TYSABRI (natalizumab) increases the risk of progressive multifocal leukoencephalopathy (PML), an opportunistic viral infection of the brain that usually leads to death or severe disability (1). This document provides information on PML in patients receiving natalizumab.

Factors That Increase the Risk of PML

Three factors that are known to increase the risk of PML in natalizumab-treated patients have been identified:

- Longer treatment duration, especially beyond 2 years.
- Prior treatment with an immunosuppressant (IS) (e.g., mitoxantrone, azathioprine, methotrexate, cyclophosphamide, mycophenolate mofetil).
- The presence of anti-JCV antibodies. Patients who are anti-JCV antibody positive have a higher risk for developing PML.

These factors should be considered in the context of expected benefit when initiating and continuing treatment with natalizumab.

US risk estimates for PML based on the known risk factors described above are presented in Table 1 (1). Data beyond 6 years of treatment are limited.

Table 1. Estimated United States Incidence of PML Stratified by Risk Factor

Anti-JCV Antibody Negative	TYSABRI Exposure†	Anti-JCV Antibody Positive	
		No Prior Immunosuppressant Use	Prior Immunosuppressant Use
<1/1,000	1-24 months	<1/1,000	1/1,000
	25-48 months	3/1,000	12/1,000
	49-72 months	6/1,000	13/1,000

Notes: The risk estimates are based on postmarketing data in the United States from approximately 69,000 TYSABRI exposed patients.
†Data beyond 6 years of treatment are limited.
The anti-JCV antibody status was determined using an anti-JCV antibody test (ELISA) that has been analytically and clinically validated and is configured with detection and inhibition steps to confirm the presence of JCV-specific antibodies with an analytical false negative rate of 3%.

PML Incidence

Global overall incidence of PML and confirmed PML cases in natalizumab-treated patients are described below and include information that is currently available. Figures 1 through 3 show PML risk estimates by treatment epoch or treatment duration, with data as of March 2017. These figures will be updated on an annual basis.

As of November 30, 2017, approximately 177,800 patients received natalizumab with a total of 618,370 patient-years of exposure in the postmarketing setting (2).

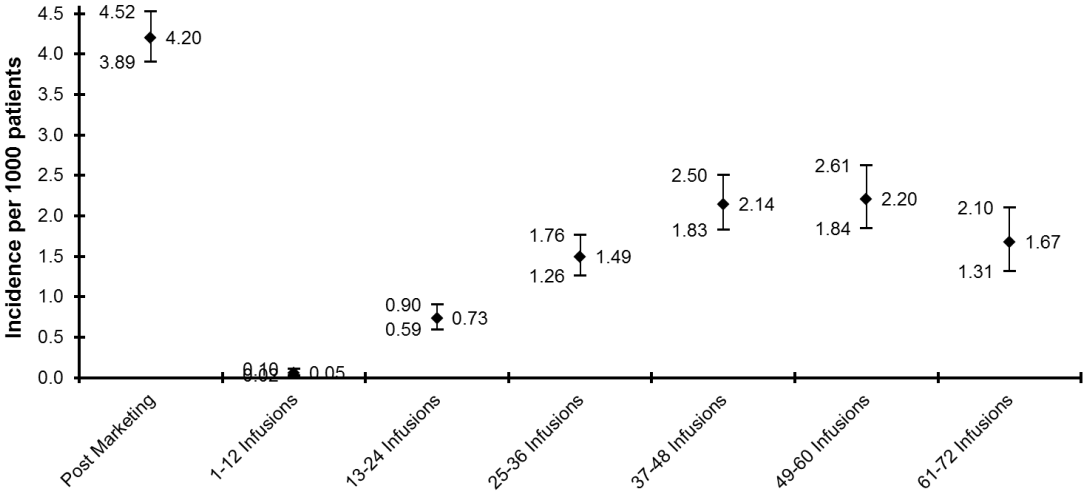
As of November 30, 2017, the global overall incidence of PML in natalizumab-treated patients is 4.19 per 1000 patients (95% CI 3.89 to 4.49 per 1000 patients) (2).

As of December 7, 2017, there have been 756 confirmed PML cases (753 MS, 3 Crohn's Disease), (205 US, 480 EEA, 71 ROW). Based on follow-up data for at least 6 months after PML diagnosis, 76.5% patients were alive with varying levels of disability. The duration of natalizumab dosing prior to PML diagnosis ranged from 8 to 136 doses. The mean duration of natalizumab dosing at the time of PML diagnosis was approximately 49 months (2).

The observed clinical trial PML incidence in patients who received a mean of 17.9 monthly doses of natalizumab was 1.00 per 1000 natalizumab-treated patients (95% CI 0.20-2.80) (3). The postmarketing rate refers to the period following the voluntary withdrawal of natalizumab from the market in 2005 and its subsequent reintroduction in 2006; it is calculated as the number of PML cases since reintroduction in patients who have had at least 1 dose of natalizumab.

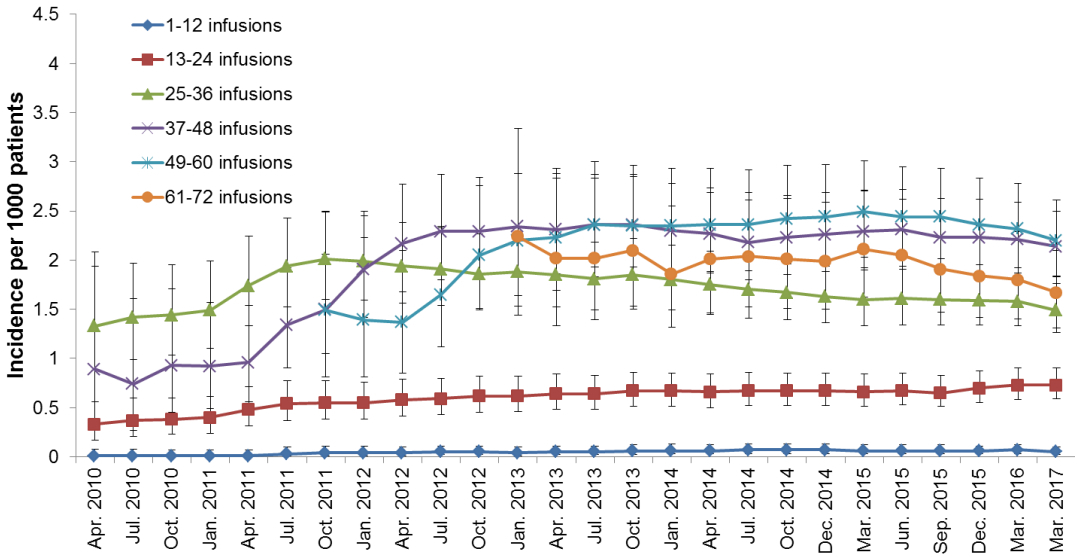
The 95% confidence interval (CI) is an estimated range that is 95% likely to include the true rate of PML. The width of the CI is an indication of the precision of the estimate. The wider the confidence intervals in relation to the point estimate indicate a higher level of uncertainty. Increasing the denominator of treated patients will increase the precision of the estimates and narrow the confidence interval.

Figure 1. Global Natalizumab PML Risk Estimates by Treatment Epoch: As of February 28, 2017



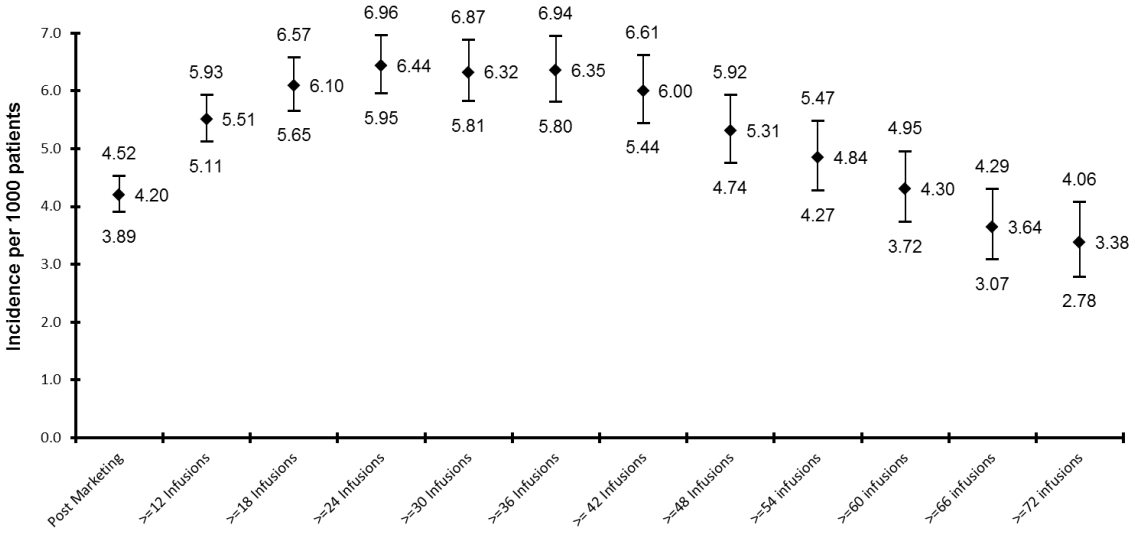
Note: This figure will be updated annually. The incidence for each epoch is calculated as the number of PML cases divided by the number of patients exposed to natalizumab (e.g., for 25 to 36 infusions, the number of all PML cases diagnosed during this period is divided by the total number of patients ever exposed to at least 25 infusions and therefore having risk of developing PML during this time) (2).

Figure 2. Estimated Global PML Risk by Treatment Epoch



Note: This figure will be updated annually. Incidence estimates by treatment epoch are calculated based on natalizumab exposure and confirmed cases of PML. Data are from the specified month as indicated and are current as of February 28, 2017. The incidence for each epoch is calculated as the number of PML cases divided by the number of patients exposed to natalizumab at each time point (e.g., for 25 to 36 infusions, the number of all PML cases diagnosed during this period is divided by the total number of patients ever exposed to at least 25 infusions and therefore having risk of developing PML during this time) (2).

Figure 3. Global Cumulative Natalizumab PML Risk Estimates by Treatment Duration: As of February 28, 2017

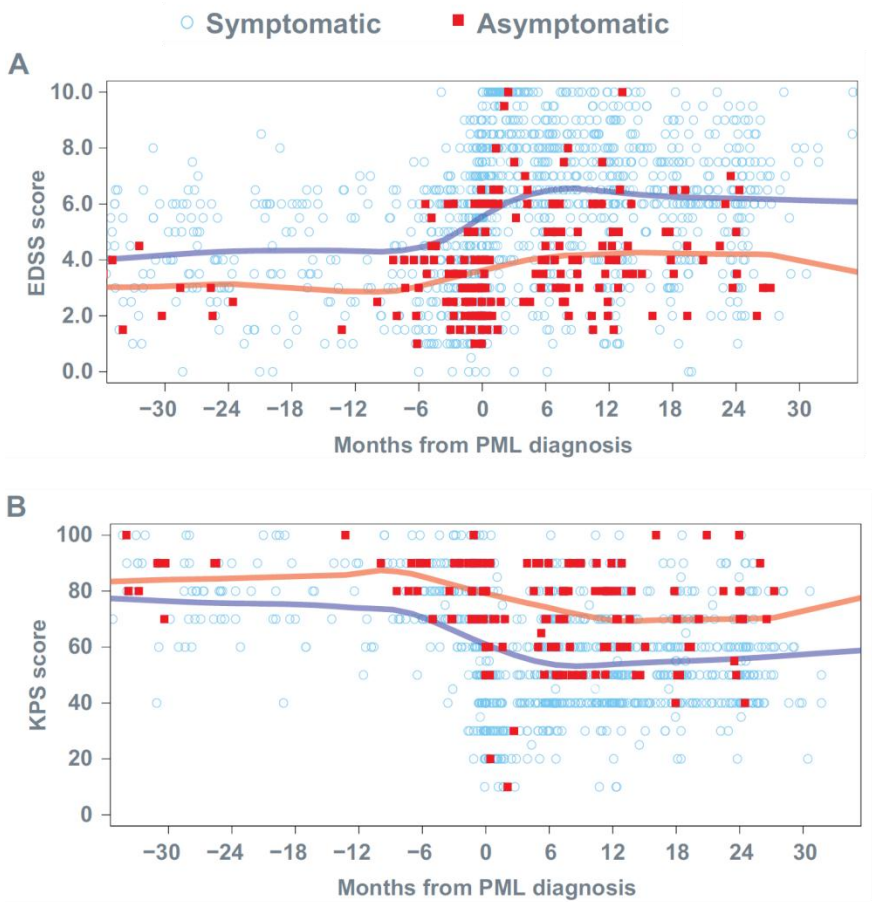


Note: This figure will be updated annually. The incidence for each time period is calculated as the number of PML cases divided by the number of patients exposed to natalizumab (e.g., for ≥ 24 infusions, all diagnosed PML cases with exposure to 24 infusions or more divided by the total number of patients exposed to at least 24 infusions) (2).

An analysis of PML data was performed as of June 4, 2015, at which time 566 PML cases had been confirmed in the postmarketing setting. Of these 566 patients 62 (11.0%) were identified as asymptomatic (defined as patients who had no clinical symptoms of PML, but had MRI findings consistent with PML and detectable JC virus DNA in the central nervous system (CNS)) and 504 (89.0%) were identified as symptomatic at PML diagnosis. As of June 4, 2015, 95.2% of asymptomatic patients and 74.2% of symptomatic patients were alive. We analyzed all available data on functional disability in asymptomatic and symptomatic PML cases (EDSS and Karnofsky scores), and observed that asymptomatic PML patients appeared to have less functional disability than did symptomatic patients prior to PML diagnosis, at diagnosis, and post diagnosis (Figure 4). This analysis is limited by the following (4):

- The number of asymptomatic PML cases in the natalizumab-treated population is relatively small.
- For some PML cases, information on patient and disease characteristics, MRI frequency, and functional outcomes is incomplete due to the nature of spontaneously reported data.
- The possibility that lead time bias might contribute to the apparent increased survival in asymptomatic patients compared with symptomatic patients cannot be ruled out.

Figure 4. Functional disability in asymptomatic and symptomatic patients with natalizumab-associated PML measured over time by (A) EDSS and (B) KPS



Weighted polynomial regression using the locally weighted scatterplot smoothing (LOWESS) algorithm. EDSS scores for asymptomatic and symptomatic PML patients are shown for time points prior to PML diagnosis, at PML diagnosis, and post PML diagnosis. Each symbol represents a single patient measurement at a single time point. EDSS scores were not available for all patients at all time points. Data prior to diagnosis were gathered from medical records. The red lines represent polynomial regression trend lines (LOWESS curves) for asymptomatic patients; the blue lines represent polynomial regression trend lines (LOWESS curves) for symptomatic patients (4).

These analyses continue to suggest that earlier detection of PML, prior to the onset of symptoms, is associated with favorable survival and functional outcomes compared with PML diagnosis after the onset of symptoms. These data also reaffirm that MRI is a valuable and sensitive tool to identify PML lesions in natalizumab-treated patients and that symptoms are not required for a PML diagnosis.

An analysis of PML outcomes was performed as of August 22, 2013, at which time there were 398 PML cases confirmed in the postmarketing setting. PML patients who were alive at the time of the analysis generally were younger at diagnosis, had less functional disability (as measured by the EDSS and KPS) prior to PML diagnosis, and had lower CSF JC viral load at the time of diagnosis. In addition, survivors had less extensive disease on MRI at diagnosis compared with

non-survivors. In general, surviving PML patients demonstrated stabilized functional disability at 6 months post PML diagnosis and remained relatively stable even beyond 18 months post PML diagnosis (5).

Patients with at least six months follow-up were studied as these patients were most likely to have reached a more stable clinical state. (Evaluation of disability after an acute event is best accomplished once the patient has reached a stable clinical state. In other neurological conditions, such as stroke, patients usually show greatest improvement within the first weeks to months, and neurological deficits generally stabilize beyond 3 to 6 months after the acute event) (6).

PML has been reported following discontinuation of natalizumab in patients who did not have findings suggestive of PML at the time of discontinuation. Patients should continue to be monitored for any new signs or symptoms that may be suggestive of PML for approximately six months following discontinuation of natalizumab.

Currently, there are no known interventions that can reliably prevent PML or adequately treat PML if it occurs. Patients treated with natalizumab must be monitored on a regular basis for signs and symptoms of PML, through clinical vigilance, neurologic assessment, and periodic MRI scans. Early diagnosis and aggressive clinical management appear to be associated with improved survival rates observed in postmarketing cases (7). In asymptomatic PML cases, better survival and functional outcomes have been described compared to patients with symptomatic PML at time of diagnosis (4, 5). The following additional factors appear to be associated with improved survival after PML (5):

- Younger age at diagnosis;
- Less functional disability prior to diagnosis;
- Lower JC viral load at diagnosis;
- More localized brain involvement by MRI at the time of diagnosis.

Anti-JCV Antibody Testing

Infection by the JC virus is required for the development of PML. Anti-JCV antibody testing should not be used to diagnose PML. Anti-JCV antibody negative status indicates that exposure to the JC virus has not been detected. Patients who are anti-JCV antibody negative have a lower risk of PML than those who are positive. Patients who are anti-JCV antibody negative are still at risk for the development of PML due to the potential for a new JCV infection or a false negative test result. The reported rate of seroconversion in patients with MS (changing from anti-JCV antibody negative to positive and remaining positive in subsequent testing) is 3 to 8 percent annually. In

addition, some patients' serostatus may change intermittently. Therefore, patients with a negative anti-JCV antibody test result should be retested periodically. For purposes of risk assessment, a patient with a positive anti-JCV antibody test at any time is considered anti-JCV antibody positive regardless of the results of any prior or subsequent anti-JCV antibody testing. When assessed, anti-JCV antibody status should be determined using an analytically and clinically validated immunoassay. Anti-JCV antibody testing should not be performed for at least two weeks following plasma exchange due to the removal of antibodies from the serum (1).

In clinical trials and on-going clinical practice, the anti-JCV antibody assay has proven to be a reliable tool for stratifying PML risk in natalizumab-treated MS patients.

- The percentage of natalizumab-treated MS PML patients with pre-PML samples, collected at least 6 months prior to PML diagnosis, testing negative for anti-JCV antibody prior to diagnosis has consistently been below the estimated false-negative rate of 2.2%, based on STRATIFY 1 study samples, which is the assay limitation (8). Among natalizumab-treated CD patients, pre-PML serum samples from the three confirmed PML cases (one from clinical trials and two postmarketing) tested anti-JCV antibody positive (2).

Summary

- Factors that increase the risk of PML have been identified: JCV exposure indicated by the presence of anti-JCV antibodies, receiving an immunosuppressant prior to receiving natalizumab, and longer treatment duration.
- As of November 30, 2017, approximately 177,800 patients received natalizumab with a total of 618,370 patient-years of exposure in the postmarketing setting worldwide.
- As of November 30, 2017, the global overall incidence of PML in natalizumab-treated patients is 4.19 per 1000 patients (95% CI 3.89 to 4.49 per 1000 patients). Based on follow-up data for at least 6 months after PML diagnosis, 76.5% patients were alive with varying levels of disability.
- Results of the anti-JCV antibody assay have been reliable in stratifying PML risk, with available pre-PML samples testing negative for anti-JCV antibody consistently falling below the 2.2% false-negative rate of the assay.
- Natalizumab-treated patients must be monitored on a regular basis for signs and symptoms of PML, through clinical vigilance, neurologic assessment, and periodic MRI scans.
- Early diagnosis and aggressive clinical management of PML appear to be associated with improved survival rates observed in postmarketing cases.
- The following factors appear to be associated with improved survival after PML:

- Younger age at diagnosis;
- Less functional disability prior to diagnosis;
- Lower JC viral load at diagnosis;
- More localized brain involvement by MRI at the time of diagnosis.

Summary of Prescribing Information: TYSABRI® (natalizumab)

Please click here: https://medinfo.biogen.com/medinfo/pdf/secure/pi/TYSABRI-pi.pdf for the full prescribing information or see the appended full prescribing information.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TYSABRI safely and effectively. See full prescribing information for TYSABRI.

TYSABRI (natalizumab) injection, for intravenous use
Initial U.S. Approval: 2004

WARNING: PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY
See full prescribing information for complete boxed warning

- **TYSABRI increases the risk of progressive multifocal leukoencephalopathy (PML), an opportunistic viral infection of the brain that usually leads to death or severe disability (5.1)**
- **Risk factors for the development of PML include duration of therapy, prior use of immunosuppressants, and presence of anti-JCV antibodies. These factors should be considered in the context of expected benefit when initiating and continuing treatment with TYSABRI (5.1)**
- **Monitor patients, and withhold TYSABRI immediately at the first sign or symptom suggestive of PML (4, 5.1)**
- **Because of the risk of PML, TYSABRI is available only through a restricted distribution program called the TOUCH® Prescribing Program (5.1, 5.2)**

----------RECENT MAJOR CHANGES ----------
Warnings and Precautions (5.1, 5.3) 08/2017

----------INDICATIONS AND USAGE ----------
TYSABRI is an integrin receptor antagonist indicated for treatment of:
Multiple Sclerosis (MS)

- TYSABRI is indicated as monotherapy for the treatment of patients with relapsing forms of multiple sclerosis. TYSABRI increases the risk of PML. When initiating and continuing treatment with TYSABRI, physicians should consider whether the expected benefit of TYSABRI is sufficient to offset this risk. See important information regarding the risk of PML with TYSABRI. (1.1, 5.1)

Crohn's Disease (CD)

- TYSABRI is indicated for inducing and maintaining clinical response and remission in adult patients with moderately to severely active Crohn's disease with evidence of inflammation who have had an inadequate response to, or are unable to tolerate, conventional CD therapies and inhibitors of TNF-α. (1.2)

Important Limitations:

- In CD, TYSABRI should not be used in combination with immunosuppressants or inhibitors of TNF-α. (1.2)

----------DOSAGE AND ADMINISTRATION ----------

- 300 mg infused intravenously over one hour, every four weeks. Do not give as an intravenous push or bolus (2.1, 2.2)
- TYSABRI solution must be administered within 8 hours of preparation (2.3)
- Observe patients during the infusion and for one hour after the infusion is complete (2.4)
- In CD, discontinue in patients that have not experienced therapeutic benefit by 12 weeks of induction therapy, and in patients that cannot discontinue chronic concomitant steroids within six months of starting therapy (2.2)

----------DOSAGE FORMS AND STRENGTH ----------
Solution [300 mg per 15 mL vial] for dilution prior to infusion (3)

----------CONTRAINDICATIONS ----------

- Patients who have or have had PML (4)
- Patients who have had a hypersensitivity reaction to TYSABRI (4, 5.3)

----------WARNINGS AND PRECAUTIONS----------

- Herpes infections: Life-threatening and fatal cases have occurred with herpes encephalitis and meningitis infections. Blindness has occurred in patients developing acute retinal necrosis. Discontinue TYSABRI if these infections occur and treat appropriately (5.3)
- Hepatotoxicity: Significant liver injury, including liver failure requiring transplant, has occurred. Discontinue TYSABRI in patients with evidence of liver injury (5.4)
- Hypersensitivity reactions: Serious hypersensitivity reactions (e.g., anaphylaxis) have occurred. Permanently discontinue TYSABRI if such a reaction occurs (5.5)
- Immunosuppression/Infections: TYSABRI may increase the risk for certain infections. Monitor patients for development of infections due to increased risk with use of TYSABRI (5.6)

----------ADVERSE REACTIONS ----------
Most common adverse reactions (incidence ≥ 10%):

- MS - headache, fatigue, arthralgia, urinary tract infection, lower respiratory tract infection, gastroenteritis, vaginitis, depression, pain in extremity, abdominal discomfort, diarrhea NOS, and rash (6.1)
- CD - headache, upper respiratory tract infections, nausea, and fatigue (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Biogen at 1-800-456-2255 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------USE IN SPECIFIC POPULATIONS----------
Pregnancy: Based on animal data, may cause fetal harm. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 08/2017

References:
TYSABRI® (natalizumab): PML Incidence in Patients Receiving TYSABRI

1. TYSABRI® (natalizumab) US Prescribing Information, I61061-24. Cambridge, MA. © Biogen. August 2017.
2. Biogen. Data on file.
3. Yousry TA, Major EO, Ryschkewitsch C, et al. Evaluation of patients treated with natalizumab for progressive multifocal leukoencephalopathy. *N Engl J Med*, 2006; 354(9): 924-33.
4. Carrillo-Infante C, Richman S, Yu B, et al. Functional and Survival Outcomes of Asymptomatic Progressive Multifocal Leukoencephalopathy in Natalizumab-Treated Multiple Sclerosis Patients: 2015 Update. Presented at: 32nd Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS), 2016 Sep 14-17; London, UK. EP1528.
5. Dong-Si T, Gheuens S, Gangadharan A, et al. Predictors of survival and functional outcomes in natalizumab-associated progressive multifocal leukoencephalopathy. *Journal of NeuroVirology*, 2015; 21(6): 637-44.
6. Kelley RE and Borazanci AP. Stroke rehabilitation. *Neurol Res*, 2009; 31(8): 832-40.
7. Richman S, Kappos L, Foley J, et al. Natalizumab-associated progressive multifocal leukoencephalopathy: survival and functional status of postmarketing cases. Presented at: 20th World Congress of Neurology (WCN), 2011 Nov 12; Marrakesh; Morocco. 1432.
8. Lee P, Plavina T, Castro A, et al. A second-generation ELISA (STRATIFY JCV DxSelect) for detection of JC virus antibodies in human serum and plasma to support progressive multifocal leukoencephalopathy risk stratification. *J Clin Virol*, 2013; 57(2): 141-6.