

Medical Information Services

TYSABRI® (natalizumab) Safety Update: (17 August 2012)

As part of our commitment to communicating information about TYSABRI (natalizumab), Biogen Idec wish to inform you of the following update.

PML Incidence in Patients Receiving TYSABRI

- As of June 30, 2012, approximately 104,300 patients have received TYSABRI in the post-marketing setting worldwide.
- As of August 1, 2012, there have been 271 confirmed cases of PML worldwide.
- Based on the 271 cases, the overall risk of PML was estimated to be 2.54 per 1000 patients (95% confidence interval: 2.24 to 2.86 per 1000 patients) (see Figure 1 and 2).

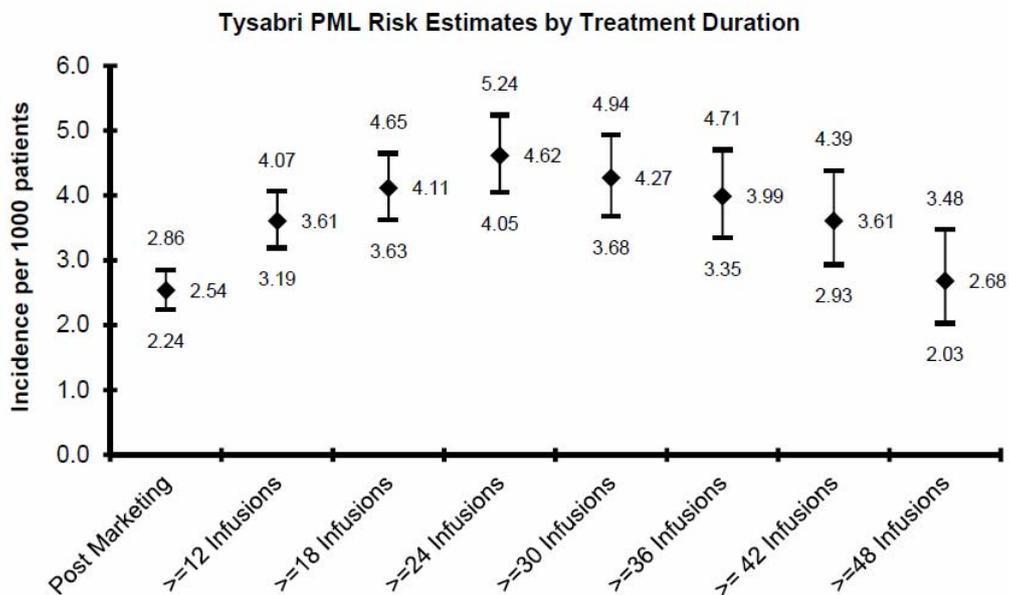
The table below shows TYSABRI utilisation and number of PML cases by region.

| Total no. of patients exposed* to TYSABRI | Total no. of TYSABRI patients diagnosed with PML | Total no. of MS and CD patients exposed* to TYSABRI (US) | Total no. of TYSABRI patients diagnosed with PML (US) | Total no. of MS patients exposed* to TYSABRI (EEA) | Total no. of TYSABRI patients diagnosed with PML (EEA) | Total no. of MS patients exposed* to TYSABRI (ROW) | Total no. of TYSABRI patients diagnosed with PML (ROW) |
|---|--|--|---|--|--|--|--|
| 104,300 | 271 | 56,612 | 97 | 39,371 | 162 | 8,275 | 12 |

US = United States; EEA = European Economic Area; ROW = Rest of World (countries other than the US or in the EEA)

*Exposure as of June 30, 2012.

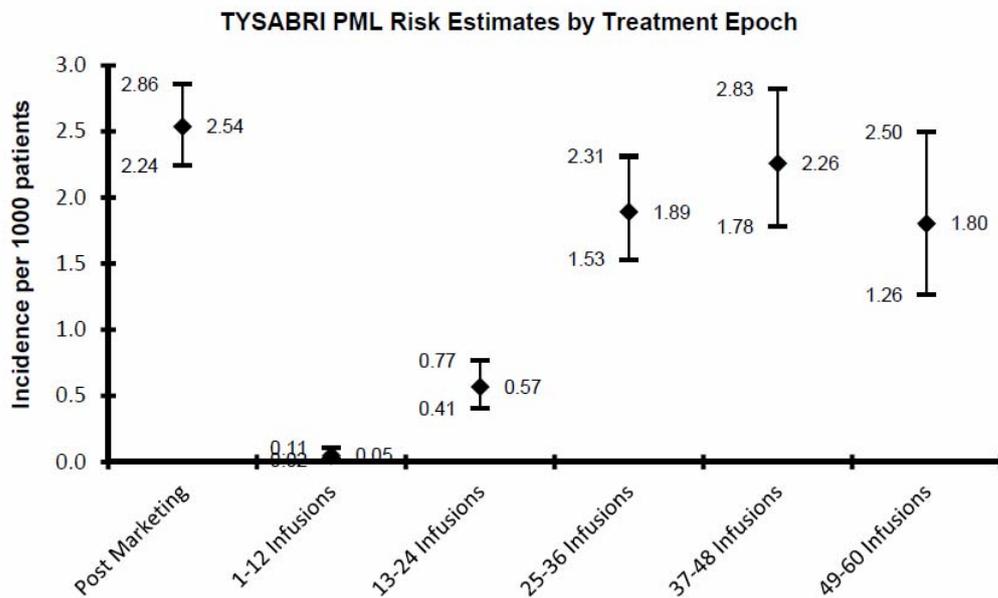
Figure 1:



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 (Yousry TA, et al. N Engl J Med. 2006;354:924-933) (1). The post-marketing rate is calculated as the number of PML cases since reintroduction in patients that have had at least 1 dose of natalizumab.

Incidence estimates by treatment duration are calculated based on TYSABRI exposure through July 31, 2012 and 271 confirmed cases as of August 1, 2012. The incidence for each time period is calculated as the number of PML cases divided by the number of patients exposed to TYSABRI (e.g. for ≥ 24 infusions all PML cases diagnosed with exposure of 24 infusions or more divided by the total number of patients exposed to at least 24 infusions). 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. There are limited data beyond four years of treatment.

Figure 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 (Yousry TA, et al. *N Engl J Med.* 2006;354:924-933) (1). The post-marketing rate is calculated as the number of PML cases since reintroduction in patients that have had at least 1 dose of natalizumab.

Incidence estimates by treatment epoch are calculated based on TYSABRI exposure through July 31, 2012 and 271 confirmed cases as of August 1, 2012. The incidence for each epoch is calculated as the number of PML cases divided by the number of patients exposed to TYSABRI (e.g. for 25 to 36 infusions 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). 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. There are limited data beyond four years of treatment.

Each of the following risk factors is associated with an increased risk of PML.

- Treatment duration, especially beyond 2 years. There is limited experience in patients who have received more than 4 years of TYSABRI treatment therefore the risk of PML in these patients cannot currently be estimated.
 - See the PML incidence graphs for the supportive data.
- Immunosuppressant (IS) use prior to receiving TYSABRI.
 - Based on data that showed that 42% (out of the first 102 post-marketing PML cases) of TYSABRI patients with PML had been treated with an IS prior to receiving TYSABRI*. As of November 23, 2010, from TYGRIS, it was estimated that 20.3% of TYSABRI-treated patients (13.9% in US and 23.6% in EU) had been treated with an IS prior to receiving TYSABRI. This indicated a disproportionate representation of prior IS use in the patients with PML compared to the TYSABRI-treated population overall, suggesting that patients treated with an IS prior to receiving TYSABRI have an increased risk of PML.
- The presence of anti-JCV antibodies.

Patients who are anti-JCV antibody positive are at an increased risk of developing PML compared to patients who are anti-JCV antibody negative. Patients who have all three risk factors for PML (i.e., have received more than 2 years of TYSABRI therapy, and have received prior immunosuppressant therapy and are anti-JCV antibody positive) have the highest risk of PML at approximately 10 in 1,000 patients treated. The risks and benefits of continuing treatment with TYSABRI should be carefully considered in patients who have all three of these risk factors for PML (2).

As of August 1, 2012, 59 of 271 (22%) of the patients with PML have died; the patients who are alive have varying levels of disability, ranging from severe to moderate to mild. PML usually leads to death or severe disability. Based on preliminary data collected from the first 175 postmarketing PML cases as of October 21, 2011, in 58 patients who were alive with at least 6 months of follow-up time since PML diagnosis and with available functional outcome data provided, ~10% had mild disability (Karnofsky score of 80 to 100), ~50% of patients had moderate disability (Karnofsky score of 50 to 70), and ~40% of patients had severe disability (Karnofsky score of 10 to 40). After 6 months, the majority of patients with severe disability (21/23, 91%) had Karnofsky scores of 40, which is at the interface between moderate and severe disability. Additionally, in the 28 patients who were alive with at least 9 months of follow-up time since PML diagnosis and with available functional outcome data provided, ~11% had mild disability (Karnofsky score of 80 to 100), ~57% of patients had moderate disability (Karnofsky score of 50 to 70), and ~32% of patients had severe disability (Karnofsky score of 10 to 40). Karnofsky scores pre-PML were reported for very few patients (n=19); the average change in Karnofsky score following PML for these 19 patients was a decrease by 26 in Karnofsky score (3). 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

* Based on 39 out of 93 patients with PML as of 4 March 2011 (Prior IS status was unknown for 9 patients and they were excluded from the analysis); did not include corticosteroids

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 stabilise beyond 3 to 6 months after the acute event) (4).

Currently, there are no known interventions that can reliably prevent PML or adequately treat PML if it occurs.

Biogen Idec remains committed to updating the MS community about the safety profile of TYSABRI. We will continue to communicate updates on TYSABRI safety through our Medical Affairs department, as well as through major medical meetings and other company-sponsored channels. Should you have any query, please do not hesitate to contact the Biogen Idec Medical Department on 1800 852 289.

References:

1. Yousry TA, Major EO, Ryschewitsch C, et al. Evaluation for progressive multifocal leukoencephalopathy in patients treated with natalizumab. *N Engl J Med.* 2006; 354: 924-933.
2. TYSABRI® (natalizumab) approved Product Information, 12 December 2011
3. Data on file, Biogen Idec
4. Kelley RE, Borazanci AP. Stroke rehabilitation. *Neurol Res.* 2009; 31: 832-840

Please refer to the Product Information before prescribing (located on the Resources page of this site or on request from Biogen Idec).

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