Date: 8th March 2016

Natalizumab (TYSABRI): Updates to PML risk minimisation measures

Dear Healthcare Professional,

In agreement with the European Medicines Agency (EMA) and the Healthcare Products Regulatory Agency (HPRA), Biogen would like to remind you of the key measures to minimise the risk of progressive multifocal leukoencephalopathy (PML) in patients receiving TYSABRI and inform you of some important new measures that may aid in earlier identification of PML with the goal of further improving outcomes in those patients that develop PML.

Summary

- **Recent analyses suggest that:**
  - **Early detection of PML is associated with improved outcomes and**
  - **PML which is clinically asymptomatic at diagnosis can represent unilobar disease on MRI more often than symptomatic PML, with a higher survival rate and better clinical outcome.**
- **More frequent MRIs (e.g. every 3-6 months) using an abbreviated MRI protocol (FLAIR, T2-weighted and DW imaging) should be considered for patients at higher risk of PML.**
- **In patients who have not received prior immunosuppressant therapy and are anti-JCV antibody positive, the level of anti-JCV antibody response (index) is associated with the level of risk for PML.**
  - **Current evidence suggests that the risk of PML is low at index value ≤0.9, and increases substantially at values above 1.5 in patients who have been on treatment with TYSABRI for longer than 2 years.**
- **Patients at higher risk of PML include those who:**
  - **Are anti-JV antibody positive, have received more than 2 years of Tysabri therapy and have received prior immunosuppressant therapy or**
  - **Have high anti-JCV antibody response (index), have received more than 2 years of TYSABRI therapy and have no prior history of immunosuppressant therapy.**
- **Patients with low anti-JCV antibody index values and no history of prior immunosuppressant use should be retested every 6 months once they reach the 2-year treatment point.**

Further detailed recommendations will be given in the educational material which is currently under preparation and will be distributed separately. For a summary please see annex 1.

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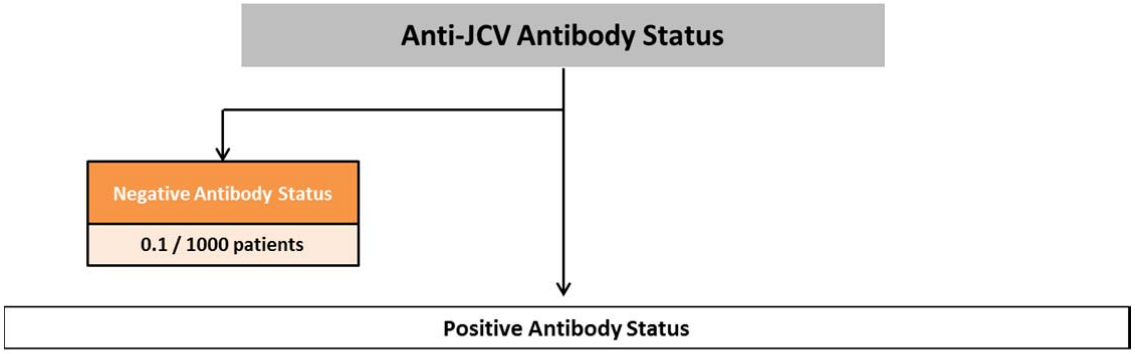
Background on the safety concern

The risk of PML in patients receiving TYSABRI is already known to be higher in patients who are serum anti-JCV antibody positive, who have prior exposure to immunosuppressant therapy, and with increasing duration of TYSABRI exposure (especially after 2 years).

Updated risk estimates for PML in TYSABRI treated patients are available from several large clinical studies (see below). For patients with no prior immunosuppressant use, the table now includes information on the association between anti-JCV antibody response (index) and risk of developing PML.

Figure 1 Updated risk estimates for PML in Tysabri treated patients



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

PML risk estimates in anti-JCV antibody positive patients were derived using Life Table method based on the pooled cohort of 21,696 patients who participated in the STRATIFY-2, TOP, TYGRIS and STRATA clinical studies. Further stratification of PML risk by anti-JCV antibody index interval for patients with no prior history of immunosuppressant use were derived from combining the overall yearly risk with the antibody index distribution. The risk of PML in anti-JCV antibody negative patients was estimated based on post-marketing data from approximately 125,000 exposed patients.

The Physician Information and Management Guideline includes comprehensive information on the diagnosis, risk stratification and treatment of PML. This is being updated with the estimation of PML risk in the different patient subgroups. Treatment initiation & continuation forms and the Patient Alert Card are also being updated and a treatment discontinuation form is being introduced.

[The summary of product characteristics (SmPC) and package leaflet (PL) will also be updated.]

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Call for reporting

Healthcare professionals should report any suspect adverse reactions associated with the use of TYSABRI in accordance with the national requirements via the national spontaneous reporting system, to:

HPRA Pharmacovigilance, Earlsfort Terrace, IRL – Dublin 2; Tel: +353 1 676 4971; Fax: +353 1 676 2517; Website: www.hpra.ie; e-mail: medsafety@hpra.ie.

ADRs can also be reported to the Marketing Authorisation Holder (MAH) by telephone (1800 812 719), fax [+44 (0) 1748 828801] or email (biogen@professionalinformation.co.uk).

Company contact point

Contact point details for further information are given in the product information of the medicinal product (SmPC and PIL) at http://www.ema.europa.eu/ema/.

Yours faithfully

Dr Fiona Thomas MBChB
Medical Director, UK and Ireland

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Annex 1

The following actions are recommended to minimise the risk of PML:

- **Before starting treatment with TYSABRI:**
  - Counsel patients and caregivers on the risk of PML, using the Treatment Initiation Form.
  - Inform them of the possible early clinical symptoms to be aware of and the need to report these urgently, should any occur.
  - Perform a baseline anti-JCV antibody test to support PML risk stratification. Before initiation of treatment, a recent (usually within 3 months) baseline MRI should be available as a reference.
- **During treatment with TYSABRI:**
  - Monitor patients clinically at regular intervals for signs and symptoms of new neurological dysfunction (e.g. motor, cognitive or psychiatric symptoms).
  - Perform a full brain MRI at least yearly for the duration of treatment.
  - Consider PML in the differential diagnosis of any patient presenting with neurological symptoms and/or new brain lesions in MRI. Note that cases of asymptomatic PML based on MRI and positive JCV DNA in the CSF have been reported.
  - Perform anti-JCV antibody testing every 6 months in antibody-negative patients. Patients who have low index values and no history of prior immunosuppressant use should also be retested every 6 months once they reach the 2-year treatment point.
  - After 2 years of treatment, re-inform patients about the risk of PML with TYSABRI.

  For patients at higher risk of PML:

  More frequent brain MRI screening for PML (e.g., every 3-6 months) should be considered using an abbreviated MRI protocol (that includes FLAIR, T2-weighted and DW imaging): earlier detection of PML in asymptomatic patients is associated with improved PML outcomes.
  - If PML is suspected, the MRI protocol should be extended to include contrast-enhanced T1-weighted imaging and testing of CSF for the presence of JCV DNA using ultrasensitive PCR testing should be considered.
  - Occasionally, in particular in patients with small lesions, exclusively grey matter involvement of PML in MRI has been observed.

If PML is suspected at any time:

- Stop treatment with TYSABRI and investigate appropriately until PML has been excluded.

After discontinuation of TYSABRI:

- Counsel patients and caregivers to continue to be aware of the risk of PML for up to 6 months following discontinuation, using the Treatment Discontinuation Form
- The existing MRI monitoring protocol should continue for an additional 6 months, as PML has been identified in patients during this time period after stopping.

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