NOTIFICATION TO THE PRAC/EMA SECRETARIAT OF A REFERRAL UNDER ARTICLE 20 OF REGULATION (EC) 726/2004
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This notification is a referral under Article 20 of Regulation (EC) 726/2004 to the PRAC made by the European Commission:

Product Name(s) Procedure name	Tysabri (natalizumab)
Active Substance(s)	Natalizumab
Pharmaceutical form(s)	All
Strength(s)	All
Route of administration(s)	All
Marketing Authorisation Holder	Biogen Idec Limited

Background

Tysabri (natalizumab–EMEA/H/C/000603) was approved in the EU on 27 June 2006. Tysabri is indicated as single disease modifying therapy in highly active relapsing remitting multiple sclerosis for the following patient groups:

- Adult patients aged 18 years and over with high disease activity despite treatment with a beta-interferon or glatiramer acetate.
  These patients may be defined as those who have failed to respond to a full and adequate course (normally at least one year of treatment) of beta-interferon or glatiramer acetate. Patients should have had at least 1 relapse in the previous year while on therapy, and have at least 9 T2-hyperintense lesions in cranial Magnetic Resonance Image (MRI) or at least 1Gadolinium-enhancing lesion. A "non-responder" could also be defined as a patient with an unchanged or increased relapse rate or ongoing severe relapses, as compared to the previous year.
  or
- Adult patients aged 18 years and over with rapidly evolving severe relapsing remitting multiple sclerosis defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI.

Use of Tysabri has been associated with an increased risk of progressive multifocal leukoencephalopathy (PML), an opportunistic infection caused by John Cunningham Virus (JCV), which may be fatal or result in severe disability. The following risk factors are associated with an increased risk of PML:

- The presence of anti-JCV antibodies;
- Treatment duration, especially beyond 2 years;
- Immunosuppressant use prior to receiving Tysabri.

Patients who have all three risk factors for PML have a significantly higher risk of PML.

Therefore a number of risk minimisation measures in relation to PML are in place for Tysabri.

Issues to be considered

Scientific evidence on PML is rapidly growing. The European Medicines Agency was made aware of new elements in relation to three key issues: risk estimates; the diagnosis of PML before the development of clinical symptoms; and anti JCV antibodies.

1) Risk estimates

Decisions on initiation and continuation of treatment by physicians and patients are currently based on an algorithm included in the educational material, and in which the estimated PML incidences are calculated in a static way and by pooling data from all sources (clinical studies, registries, spontaneous reports). The interim data from the STRATIFY 2[1] study for patients with positive anti-JVC antibody status with and without a history of immunosuppressive treatment seems to indicate a higher risk of PML based on Kaplan Meier curves than currently described in the algorithm. It is therefore appropriate to review the calculations to ensure that accurate risk estimates are available for treatment decisions.

[1] JCV Antibody Program in Patients With Relapsing Multiple Sclerosis Receiving or Considering Treatment With Tysabri: STRATIFY-2.

2) Diagnosis of PML before the development of clinical symptoms
As of 16 August 2014, 45 of 490 confirmed PML cases (9.2%) were clinically asymptomatic at the time of PML diagnosis. Asymptomatic PML patients are associated with unilobar lesions reflecting a more localised disease. The data also seems to indicate that asymptomatic PML cases have a higher survival rate (95.6%) compared with symptomatic cases (77.1%).

Current recommendations are for a MRI to be performed within 3 months before treatment initiation, and annually thereafter. Recent literature suggests that more frequent MRI testing may contribute to increase the proportion of cases detected in the asymptomatic stage[2,3].

3) Anti JCV antibodies
Initial interpretations of the serological anti-JCV antibody test suggested that a negative status could be used to reassure patients that the probability of developing PML is very low (approximately 1/10000). However longitudinal serological follow-up from the combined AFFIRM[4] and STRATIFY-1[5] studies showed that nearly 13% of patients who were anti-JCV antibody negative at baseline could become positive during follow-up. Therefore, negative JCV serology at treatment initiation is not sufficient for long-term reassurance. The current recommendation in the product information is to retest these patients every 6 months for antibodies. Since this recommendation was put in place, a more sensitive second generation ELISA assay has been developed, and there is a need to assess whether this has an impact on current recommendations for antibody testing.

In addition, in the literature it is suggested that an anti-JCV antibody index >1.5 may be interpreted as a risk factor for PML[6], therefore, it may be necessary to review the surveillance strategy when therapy is pursued.

In view of the above, the European Commission (EC) initiates a procedure under Article 20 of Regulation (EC) No 726/2004 and requests the Agency to assess the above elements and their potential impact on the benefit risk balance for the centrally authorised medicinal product Tysabri. The EC requests the Agency to give its opinion by 31 January 2016 on whether a regulatory action with regard to the marketing authorisation for this product is necessary.

As the request results from the evaluation of data resulting from pharmacovigilance activities, the opinion should be adopted by the Committee for Medicinal Products for Human Use on the basis of a recommendation of the Pharmacovigilance Risk Assessment Committee.

[redacted]

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Medicinal products authorisations, European Medicines Agency

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2 Mc Govern EM, Hennessy MJ. Asymptomatic progressive multifocal leukoencephalopathy associated with natalizumab. J Neurol (2013) 260:665–7. doi:10.1007/s00415-012-6759-0.

3 Phan-Ba R, Lommers E, Tshibanda L, Calay P, Dubois B, Moonen G, et al. MRI preclinical detection and asymptomatic course of a progressive multifocal leucoencephalopathy (PML) under natalizumab therapy. J Neurol Neurosurg Psychiatry (2012) 83:224–6. doi:10.1136/jnnp-2011-300511.

4 A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study to Determine the Safety and Efficacy of Natalizumab in Subjects With Relapsing-Remitting Multiple Sclerosis: AFFIRM.

5 JCV Antibody Program in Patients With Relapsing Multiple Sclerosis Receiving or Considering Treatment With Tysabri: STRATIFY-1.

6 Plavina T, Subramanyam M, Bloomgren G, Richman S, Pace A, Lee S, et al. Anti-JC virus antibody levels in serum or plasma further define risk of natalizumab-associated progressive multifocal leukoencephalopathy. Ann Neurol (2014) 76(6):802–12. doi:10.1002/ana.24286.