07 May 2015
EMA/PRAC/293316/2015

PRAC List of questions

To be addressed by the marketing authorisation holder

Article 20 of Regulation (EC) No 726/2004 resulting from pharmacovigilance data

Invented name: Tysabri

INN: natalizumab

Procedure number: EMEA/H/A-20/1416/C/000603/0083

Marketing authorisation holder: Biogen Idec Limited

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The presence of serum antibodies against John Cunningham virus (JCV), the duration of natalizumab treatment, and the history of immunosuppressant therapy prior to natalizumab treatment are known risk factors for development of progressive multifocal leukoencephalopathy (PML). However, these risk factors do not allow a reliable individual prediction of PML. Thus, more precise strategies to quantify individual PML risk among natalizumab-treated patients are considered necessary. Therefore, the MAH is requested to analyse whether new scientific knowledge and progressively accumulated evidence needs to be translated into additional risk minimisation measures for multiple sclerosis (MS) patients treated with natalizumab.

Diagnosis of PML before the development of clinical symptoms

1. Until now approximately 11 % of all PML patients were found to be asymptomatic, whereas approximately 89 % of PML patients had clinical symptoms of PML when they were diagnosed. Survival rate of asymptomatic patients is apparently higher than of symptomatic patients. The MAH is asked to provide an analysis of asymptomatic and symptomatic PML cases (at the time of diagnosis) after natalizumab considering but not limited to the following points:
    a. Rate of asymptomatic and symptomatic PML patients who survived
    b. Update of disability outcomes of asymptomatic and symptomatic patients with regard to change of Karnofsky score and expanded disability status scale (EDSS) score prior to PML diagnosis and at the latest follow up time point
    c. An analysis of the frequency of MRI testing of asymptomatic and symptomatic PML patients
    d. The interval between the last MRI without signs for PML and first symptoms in symptomatic PML patients related to the outcome (survival, death)

    Please stratify by patients characteristics, such as but not limited to age, prior immunosuppressant treatment, duration of natalizumab treatment, duration of MS, PML extent on MRI at diagnosis of PML, time interval between first suspected MRI and onset of symptoms to PML diagnosis, EDSS score and Karnofsky score at baseline (or while on natalizumab treatment) and prior to PML diagnosis.

    The MAH should consider how these data impact on current recommendations for frequency of MRI testing, depending on the PML risk factors.

2. Almost all PML patients were diagnosed while on natalizumab treatment, some patients have been diagnosed after discontinuation of natalizumab. Please provide a calculation and analysis of the risk of PML after discontinuation of natalizumab and the time interval to reconstitution of the immune system. In this context, please also consider the time interval between discontinuation of natalizumab treatment and first symptoms/time to diagnosis (for asymptomatic patients) as well as the treatment for multiple sclerosis at the time of PML diagnosis.

Anti JCV antibodies

3. Anti-JCV antibody index was suggested as a marker of PML risk[1]. Please provide available data concerning antibody index and risk of PML from ongoing and completed studies, including individual longitudinal data and justification for the cut off of the antibody index. The MAH should discuss the need to update the risk minimisation measures in light of this review.

4. The current PML algorithm is based on the first generation ELISA anti-JCV antibody assay. Please provide seroprevalence data for the second generation ELISA anti-JCV antibody assay by age, history of MS treatment and country (e.g. JEMS study[2]). Annual seroconversion rate from negative to positive and vice versa should also be provided. The performance criteria of the second generation anti-JCV antibody assay should be presented. Please provide an analysis of the impact of the second generation assay on the PML algorithm as currently reflected in the educational material. In light of the accumulating data, the MAH should consider whether the current testing/retesting schedule for seronegative patients should be amended.

Risk estimates and risk stratification

5. Please provide an updated calculation (including 95% CI) of incidence and Kaplan Meier Curves for PML risk stratified by anti-JCV status and history of immunosuppressant treatment from clinical trial and observational studies (e.g. STRATIFY2, TOP, Tygris, STRATA). If appropriate, consider to stratify also according to the antibody index.
   a. Kaplan Meier Curves for individual studies and combined studies should be presented.
   b. Please justify why incidence rates rather than Kaplan Meier curves are presented in the Physician Information and Management Guideline.

6. A multicentre European study found that natalizumab-treated patients who developed PML had low levels of L-selectin (CD62L)-expressing CD4+ T cells prior to diagnosis[3]. The MAH should review all relevant evidence from available sources to evaluate whether L-selectin expression on CD4+ T cells may be another valid risk factor and consider the need for additional risk minimization measures based on this analysis.

7. Please discuss, based on the latest scientific evidence, whether there are additional possible risk markers for PML development and the potential impact on the current risk minimisation measures.

8. Please provide a proposal and justification for any additional risk minimisation measures which may improve the benefit-risk balance of natalizumab and how their effectiveness should be monitored.

[1] 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.
[2] Bozic, C., Subramanyam, M., Richman, S., Plavina, T., Zhang, A. and Ticho, B. (2014), Anti-JC virus (JCV) antibody prevalence in the JCV Epidemiology in MS (JEMS) trial. European Journal of Neurology, 21: 299–304.
[3] Schnabl N et al. L-selectin is possible bio marker for individual PML Risk in natalizumab-treated MS patients. Neurology 2013, 81(10):865-71