# Annex IV

## Scientific conclusions

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Scientific evidence on progressive multifocal leukoencephalopathy (PML) in patients treated with Tysabri is rapidly growing. New information has become available on three key issues: risk estimates; the diagnosis of PML before the development of clinical symptoms; and anti-JC virus antibodies. There is a need to consider whether regulatory action is necessary in light of the new elements.

In view of the above, on 29 April 2015 the European Commission triggered a procedure under Article 20 of Regulation (EC) No 726/2004, and asked the Agency to assess the above elements and their potential impact on the benefit-risk balance of Tysabri. The EC requested the Agency to give its opinion 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 (CHMP) on the basis of a recommendation from the Pharmacovigilance Risk Assessment Committee (PRAC).

**Overall summary of the scientific evaluation by the PRAC**

Natalizumab is a humanized monoclonal antibody targeting the α-chain of the α4β1 adhesion molecule. Tysabri (natalizumab) was approved in the EU on 27 June 2006 and is currently indicated as single disease modifying therapy in highly active relapsing remitting multiple sclerosis (MS).

Natalizumab is associated with the onset of progressive multifocal leukoencephalopathy (PML), which is caused by John Cunningham Virus (JCV). The onset of PML in MS has serious prognostic implications, as it leads to death in about 20% of patients or to serious disability in 40% of survivors. The clinical presentation of natalizumab-associated PML is considered not distinct from classical PML, and consists in cognitive disorders in more than half of the patients together with motor symptoms, ataxia, neurovisual disturbances, and dysphasia or agnosia in more than 40% of cases.

Since the auhtorisation of natalizumab, three main risk factors for PML have been identified:

- the presence of JCV-specific antibodies,
- the increasing duration of treatment (treated > 24 months),
- a history of immunosuppressive therapy.

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.

*Diagnosis of PML before development of clinical symptoms*

As of May 2015, 142,958 patients had received natalizumab worldwide with 432,814 patient-years of exposure. A total of 566 PML cases have been reported globally as of 04 June 2015, of which 133 patients died (23.5 % 0f PML patients). Patients who survive often have serious morbidity associated with serious and permanent disability.

In sixty-two PML patients (10.9%) asymptomatic onset PML has been reported. While 10 cases have been reported in the US, most of the asymptomatic cases were reported from EU/ROW (83%, 52/62). Although asymptomatic PML patients had generally similar baseline clinical characteristics compared with symptomatic patients, a higher proportion of asymptomatic patients presented with more localized disease (64% unilobar PML) on Magnetic Resonance Image (MRI) at the time of diagnosis compared to symptomatic PML patients (36%). The shorter time to diagnosis of

asymptomatic patients compared with symptomatic patients may have enabled earlier immune reconstitution following discontinuation of natalizumab. Most importantly, in terms of outcomes, asymptomatic patients appeared to have less accrual of disability over time and higher survival rates compared with symptomatic patients (95% vs. 74%). These data confirm previous observations that early PML diagnosis is critical in limiting the degree of permanent brain damage before immune reconstitution can be achieved, and reinforces the need to put in place strategies for the earliest possible identification of potential PML cases, if possible before the development of clinical symptoms of PML.

Asymptomatic PML cases were identified via routine MRI. MRI is considered to be a sensitive method to identify even small and asymptomatic PML lesions. Considering the dire diagnosis of PML a high level of vigilance and a low threshold even for invasive diagnostic measures and interventions such as MRI is warranted for managing patients with high risk for PML development. In spite of limitations of the currently available evidence such as small numbers, lack of information about MRI frequency in PML patients, false positive and false negative rate of MRI screenings, patients with a high risk for PML development may in particular benefit from more frequent MRIs because periodic brain MRI are likely to provide earlier detection of PML, even before symptoms develop, and subsequently better outcomes.

Published data suggest that patients considered as having a high risk for PML development and who continue natalizumab treatment beyond 2 years of treatment may benefit from more frequent MRI screening e.g. every 3 to 6 months.

There seems to be consensus among experts that routine MRI screening for suspected PML lesions can be conducted without gadolinium–enhancement. For natalizumab-treated patients with MS, who are at high risk of PML, brain MRI screening using a protocol that includes FLAIR (fluid-attenuated inversion recovery), T2-weighted and diffusion –weighted imaging is recommended. Increasing evidence indicates that T2-FLAIR is the most sensitive sequence for detecting PML. Diffusion –weighted imaging is highly sensitive for depicting acute demyelinisation and can also aid differentiation of acute PML lesions from chronic and subacute demyelinating PML lesions. In patients with MRI lesions suggestive for PML, the MRI protocol should be extended to include contrast-enhanced T1-weighted imaging to detect inflammatory features and the possible coincidence of PML and PML-IRIS (Immune Reconstitution Inflammatory Syndrome), particularly during follow up.

It is acknowledged that high expertise is necessary to identify small and asymptomatic PML lesions via MRI. Thus, adequate guidance needs to be provided in the educational materials, and other tools may also be explored (e.g. web-based) for sharing MRIs and consultation of additional expertise.

*Anti-JCV antibody index for guiding MRI monitoring frequency*

Available data to date suggest that anti-JCV antibody index is correlated with the risk of PML in anti-JCV antibody positive patients with no prior immunosuppressant use. However, it is unclear whether a single index cut-point can be identified within the range of index thresholds assessed that will provide optimal clinical utility in terms of treatment decisions. The balance between sensitivity and specificity in this range needs to be carefully considered. Sensitivity differs very little between the index of 0.9 and 1.5 but there is improved specificity with 1.5. Currently available evidence suggests that the risk of PML is low at an index equal to or below 0.9 (and lower than previously estimated) and increases substantially above 1.5 for patients who have been on treatment with Tysabri for longer than 2 years. For patients with prior immunosuppressant treatment, no significant difference was observed in median index between non-PML and PML patients.

*Anti-JCV antibody testing*

Currently it is recommended that patients who are anti-JCV antibody negative should be tested for seroconversion twice yearly. Based on the data on antibody index stability from STRATIFY-2 the recommendation should be maintained.

In addition patients without prior immunosuppressant use and a low antibody index should also be tested every 6 months if they are treated beyond 2 years. For patients without prior immunosuppressant use and with high anti-JCV antibody index, no further antibody testing is required, as more frequent MRI screening should be considered if natalizumab treatment is continued for more than 2 years.

*Anti-JCV antibody ELISA*

The assumption of 55% positive serostatus for the overall natalizumab-treated population utilized in the PML risk algorithm calculations remains acceptable. In general, the positive serostatus results using the first and second generation assays were similar. There is no significant impact of the second generation assay on the risk estimates within the algorithm.

Considering real world data from UNILABS from four EU countries showing that the upper annual serostatus change rate can be as high as 16%, the annual (negative to positive) serostatus change rate in the Physician Information and Management Guidelines needs to be updated. In addition, it needs to be clarified that patients who test anti-JCV antibody positive at any time should be considered to beat an increased risk of PML, independent of any prior or subsequent antibody test result.

*PML development after discontinuation of natalizumab*

All PML cases in patients who had received natalizumab occurred within 6 months of the last infusion. These findings support the current SmPC recommendation that physicians should remain vigilant for signs and symptoms of PML for approximately 6 months after natalizumab discontinuation, and that the same monitoring strategy should apply for up to 6 months after discontinuation. It is important to update the package leaflet concerning the risk of PML up to 6 months following Tysabri discontinuation.

*PML risk estimation*

The risk stratification algorithm in the educational material will be revised to include current estimates derived from a pooled study cohort (STRATIFY-2, TOP, TYGRIS and STRATA studies) of natalizumab-treated patients, and to incorporate anti-JCV antibody index.

Supplemental presentations of PML risk using different methodologies may be complementary to the information within the current algorithm and will provide additional information to physicians as they engage in benefit/risk discussions with their patients. In particular, the inclusion of a Kaplan-Meier analysis of PML risk alongside the algorithm would allow to present cumulative risk of PML over time.

*Biomarkers for PML development*

Recent efforts to identify potential biomarkers are promising but have not resulted, to date, in the identification of new markers that can be used in clinical practice to enhance the existing PML risk stratification.

In view of all of the above, the PRAC concluded that the benefit-risk balance of Tysabri remains favourable subject to amendments to the product information and additional risk minimisation measures as described below.

The PRAC adopted a revised version of the Risk Management Plan (RMP) reflecting the amendments agreed during the procedure.

The PRAC agreed on the need to amend the physician information and management guideline and updated the key elements of the educational material accordingly. A mock-up of the updated physician information and management guideline can be found annexed to the RMP. In addition, the patient alert card and the treatment initiation and continuation forms are also updated, and a new treatment discontinuation form is introduced.

The wording of a Direct Healthcare Professional Communication has been adopted, together with a communication plan.

**Grounds for PRAC recommendation**

Whereas

- The PRAC considered Tysabri (natalizumab) in the procedure under Article 20 of Regulation (EC) No 726/2004, initiated by the European Commission
- The PRAC reviewed all data presented by the MAH on the risk of PML in association with Tysabri, as well as other data made available during the procedure and the views expressed by the neurology scientific advisory group.
- The PRAC concluded that PML which is clinically asymptomatic at diagnosis represents more frequently localised disease in MRI, with a higher survival rate and better clinical outcome as compared to symptomatic PML. Early diagnosis of PML appears to be associated with improved outcomes.
- As a consequence, the PRAC recommended that more frequent MRI screening for PML (e.g. every 3-6 months) using an abbreviated MRI protocol should be considered in patients at higher risk of development of PML.
- The PRAC also concluded that, 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 risk of developing PML. Current evidence suggests that risk increases with increasing antibody index but there is no clear cut off value. In patients treated for longer than 2 years, the risk of PML is low at index values of 0.9 or less, and increases substantially at values above 1.5.
- The PRAC recommended that patients with low anti-JCV antibody index who have not received prior immunosuppressant therapy should be retested every six months once they reach the 2-year treatment point.
- The PRAC also considered it necessary to update the existing educational material, particularly in relation to the risk estimates for development of PML in Tysabri-treated patients.

In view of the above, the Committee considered that the benefit-risk balance of Tysabri remains favourable subject to the agreed amendments to the product information and additional risk minimisation measures.

The Committee, as a consequence, recommended the variation to the terms of the marketing authorisation for Tysabri.

**CHMP opinion**

Having reviewed the PRAC recommendation, the CHMP agrees with the PRAC overall conclusions and grounds for recommendation.

***Overall conclusion***

The CHMP, as a consequence, considers that the benefit-risk balance of Tysabri remains favourable subject to the amendments to the product information described above.

Therefore the CHMP recommends the variation to the terms of the marketing authorisations for Tysabri.