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Committee for Medicinal Products for Human Use (CHMP)

# Tysabri

Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation

International non-proprietary name: natalizumab

Procedure No. EMEA/H/C/000603/PSUV/0062

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**Scientific conclusions**

Taking into account the PRAC Assessment Report on the PSUR for Tysabri, the scientific conclusions of PRAC are as follows:

The risk stratification algorithm for progressive multifocal leukoencephalopathy (PML) was updated within the PSUR procedure. Regarding the estimated PML incidence stratified by the three risk factors (presence of anti-JCV antibodies, longer treatment duration, immunosuppressant use prior to receiving Tysabri), the PML risk estimates included in this PSUR were similar to the PML risk estimates included in the prior PSUR. Regarding prior use of an immunosuppressant (IS) therapy as a risk factor for developing PML, the available data on the wash-out period between the last dose of IS therapy and the start of Tysabri are limited and do not permit to draw clear conclusions on the nature of prior IS therapy/ duration of wash-out period and the associated PML risk. Following a request for supplementary information, the MAH provided a Kaplan-Meier analysis of PML risk using data from the STRATIFY-2 study. The risk to develop PML increases in the subjects with prior IS significantly once treatment duration of approximately 48 months is exceeded. However, the fact, that the type of IS and the treatment free period between stopping IS and commencing Tysabri treatment is not included in this risk calculation of the PML risk assessment could also lead to the conclusion that prior IS therapy is not a risk factor and rather a confounding factor for patients to be treated with Tysabri. The MAH is therefore asked to comment on the validity and robustness of this factor for the PML risk assessment. Within the STRATIFY-2 study, the overall PML incidence using all PML cases and all Tysabri-treated patients as of February 2013 is 45/23,782 or 1.89/1,000, which is generally consistent with the overall PML incidence estimate in Tysabri-treated MS patients in the United States (US). The PRAC considered these preliminary data reassuring and recommended that such a presentation should be included in future PSURs.

Concerning JCV serology, a recently published study (Berger et al, 2013) found a considerable proportion of false negative results of the JCV serum antibody test. From the MAH viewpoint, the published data from Berger et al may overestimate the false negative rate due to the small number of study subjects used in the analysis. Although the PRAC agreed that this could be a reasonable explanation, the sensitivity of the ELISA (Enzyme-linked immunosorbent assay) tests used in the analysis of specimens from subjects enrolled in STRATIFY- 1, AFFIRM/STRATA studies may not be comparable with the ELISA tests used by Berger et. al. in subjects enrolled in STRATIFY-2 study and hence, the PRAC is of the concern that a discrepancy in the true false negative rate could underestimate the risk to develop PML in the JCV seronegative tested individuals treated with Tysabri. In addition, on the basis of data from STRATIFY-1 (over 18 months), AFFIRM (over 30 months) and STRATA (over approximately 6 years) studies and other publication (Trampe et al., 2012), the PRAC concluded that there is evidence that anti-JCV antibody prevalence increases significantly over time, which in turn would raise the question whether this increase was due to recent new infections or if it was a sign of fluctuations in serostatus. The latter indeed could indicate a change in the viral load or a change in the site of viral infections. However, if the observed increase in anti-JCV prevalence was not due to de-novo infections, it must be assumed that the false-negative rate of the assay among latently infected individuals would be much higher than estimated so far, thus questioning the sensitivity of the anti-JCV antibody assay (ELISA) test and its relevance for a reliable inclusion of test results in the risk assessment for developing PML.

Therefore, the PRAC recommended an update of section 4.4 of the Summary of Product Characteristics to include a statement that anti-JCV antibody negative patients may still be at risk of PML for reasons such as a new JCV infection, fluctuating antibody status or a false negative test result.

In addition, a re-evaluation of the risk algorithm used for PML should be presented in the next PSUR.

The CHMP agrees with the scientific conclusions made by the PRAC.

**Grounds recommending the variation to the terms of the Marketing Authorisation**

On the basis of the scientific conclusions for Tysabri, the CHMP is of the opinion that the benefit-risk balance of the medicinal product containing the active substance natalizumab is favourable subject to the proposed changes to the product information.

The CHMP recommends that the terms of the Marketing Authorisation should be varied.