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Updated recommendations to minimise the risk of the rare brain infection PML with Tysabri

New advice may help early detection of PML and improve patients' outcomes

EMA's Pharmacovigilance Risk Assessment Committee (PRAC) has completed its review of the risk of progressive multifocal leukoencephalopathy (PML) with the multiple sclerosis medicine Tysabri (natalizumab) and has recommended new measures to minimise this risk. PML is a rare and very serious brain infection caused by John Cunningham (JC) virus.

Recent studies suggest that early detection and treatment of PML when the disease is asymptomatic (is still in the initial stages and shows no symptoms) are critically important in limiting the degree of brain damage and resulting disability caused by the disease. Asymptomatic cases of PML can be detected on an MRI scan. On the basis of this data, the PRAC concluded that for patients at higher risk of PML more frequent MRI scans (e.g. every 3 to 6 months) should be considered.

Known risk factors for the development of PML in patients treated with Tysabri are the presence of antibodies against JC virus (a sign that a person has been exposed to the virus), treatment with Tysabri for more than two years, and use of immunosuppressant medicines (medicines that reduce the activity of the immune system) before starting Tysabri. Patients who have all three risk factors are considered at higher risk of PML.

New data from clinical studies suggest that, in patients who have not been treated with immunosuppressants before starting Tysabri, the level of antibodies (index) relates to the level of risk for PML. More specifically, current evidence suggests that the risk of PML is small, and lower than previously estimated, at antibody index values of 0.9 or less, and increases substantially in patients with index values above 1.5 who have been treated with Tysabri for longer than 2 years. Therefore, the PRAC concluded that patients with a high antibody index who have not used immunosuppressants before Tysabri and have been treated with Tysabri for more than 2 years are also considered at higher risk of PML.

In patients at higher risk of developing PML, treatment with Tysabri should only be continued if benefits outweigh the risks.

For patients who have a low antibody index and have not used immunosuppressant medicines before starting Tysabri, the PRAC recommends repeating the antibody test every 6 months once they have taken Tysabri for longer than 2 years.



In patients who tested negative for JC virus antibodies, the antibody test should be repeated every 6 months.

If PML is suspected at any time, treatment with Tysabri must be stopped until PML has been excluded.

The PRAC recommendation will now be forwarded to the Committee for Medicinal Products for Human Use (CHMP) for the adoption of EMA final opinion. Further details including advice for patients and healthcare professionals will be published at the time of the CHMP opinion.

More about the medicine

Tysabri is a medicine used to treat adults with highly active multiple sclerosis (MS), a disease of the nerves in which inflammation destroys the protective sheath surrounding the nerve cells. Tysabri is used in the type of MS known as 'relapsing-remitting' MS, when the patient has attacks (relapses) in between periods with no symptoms (remissions). It is used when the disease has failed to respond to treatment with a beta-interferon or glatiramer acetate (other types of medicines used in MS), or is severe and getting worse rapidly.

The active substance in Tysabri, natalizumab, is a monoclonal antibody (a type of protein) that has been designed to recognise and attach to a specific part of a protein called ' $\alpha4\beta1$ integrin'. This is found on the surface of most leucocytes (the white cells in the blood that are involved in the inflammation process). By blocking the integrin, natalizumab stops the leucocytes from going from the blood into the brain. This reduces the inflammation and nerve damage caused by MS.

Tysabri was authorised in the European Union in June 2006.

More about the procedure

The review of Tysabri was initiated on 7 May 2015 at the request of the European Commission, under Article 20 of Regulation (EC) No 726/2004.

The review has been carried out by the Pharmacovigilance Risk Assessment Committee (PRAC), the Committee responsible for the evaluation of safety issues for human medicines, which has made a set of recommendations. During its assessment, the PRAC sought the advice of a group of experts in neurology. The PRAC recommendations will now be sent to the Committee for Medicinal Products for Human Use (CHMP), responsible for questions concerning medicines for human use, which will adopt the Agency's final opinion. The final stage of the review procedure is the adoption by the European Commission of a legally binding decision applicable in all EU Member States.

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