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Questions and answers on the review of Tysabri (natalizumab)

Outcome of a procedure under Article 20 of Regulation (EC) No 726/2004

The European Medicines Agency has completed a review of Tysabri (natalizumab) at the request of the European Commission, following concerns over the safety of the medicine. The Agency's Committee for Medicinal Products for Human Use (CHMP) has concluded that the benefits of Tysabri continue to outweigh its risks, but has recommended that a number of measures be put in place to manage the risk of the brain infection progressive multifocal leukoencephalopathy (PML) and to make sure that patients and doctors are aware of this risk.

What is Tysabri?

Tysabri is a medicine that contains the active substance natalizumab. It is used to treat adults with multiple sclerosis (MS), a disease of the nerves in which inflammation destroys the protective sheath surrounding the nerve cells. It is used in the type of MS known as 'relapsing-remitting', when the patient has MS attacks in between periods with no symptoms. Tysabri is used when the disease is highly active, both in patients who have failed to respond to treatment with a beta-interferon, and in patients whose disease is severe and rapidly getting worse. It is given by infusion (drip into a vein) once a month.

The active substance in Tysabri, natalizumab, is a monoclonal antibody. It works by attaching to and blocking an 'integrin' protein that is found on the surface of most leucocytes (immune system cells involved in the inflammation process). This stops the leucocytes moving from the blood into the brain, reducing the inflammation and nerve damage caused by MS.

Tysabri has been authorised in the European Union (EU) since June 2006 and is marketed in 24 EU Member States¹.

¹ Tysabri is marketed in Austria, Belgium, Bulgaria, Cyprus, the Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Ireland, Italy, Latvia, Luxembourg, the Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden and the United Kingdom.



Why was Tysabri reviewed?

The CHMP reviewed Tysabri after it had received reports of side effects in patients receiving the medicine. These included 23 confirmed cases of PML reported worldwide between July 2008 and October 2009, resulting in four deaths. Fourteen of these cases, including one death, were reported in the EU. PML is a rare brain infection caused by a virus called the JC virus. This virus is commonly found in the general population but only leads to PML if the immune system has been weakened. Like MS, PML causes damage to the protective sheath surrounding nerves and it usually leads to severe disability or death. The symptoms of PML may be similar to those of a MS attack.

As a result of these reports, the European Commission issued a formal request in October 2009, asking the CHMP to issue an opinion on whether the marketing authorisation for Tysabri should be maintained, varied, suspended or withdrawn across the EU.

Which data has the CHMP reviewed?

The CHMP reviewed information on the benefits and risks of Tysabri provided by the marketing authorisation holder that has become available since the medicine has been authorised. It also looked at information on side effects reported from healthcare professionals and health authorities, looking in particular at the available information on patients with PML. The Committee also consulted a group of experts specialising in the treatment of brain and nervous system diseases, which included neurologists and representatives of European MS patients.

What are the conclusions of the CHMP?

The CHMP concluded that Tysabri is an effective medicine for many patients with highly active relapsing-remitting MS, when they have failed to respond to beta-interferon treatment or when the disease is severe and getting worse rapidly. There are few alternative treatments for these groups of patients.

The Committee also concluded that the risk of developing PML appears to increase when a patient has been receiving Tysabri for two years or more. By the end of the review procedure on 20 January 2010, the total number of confirmed PML cases had risen to 31 worldwide, of whom 23 had been receiving Tysabri for more than two years. This is equivalent to around one case of PML for every 1,000 patients treated with Tysabri for two years or more.

The Committee noted that there are no known ways to prevent or treat PML, so it is important that the symptoms of the disease are detected as soon as possible. Tysabri should be stopped in patients suspected of having PML, to allow the immune system to recover and begin to attack the JC virus. The CHMP noted that this can put patients at risk of immune reconstitution inflammatory syndrome (IRIS), particularly if techniques to remove the medicine from the body more quickly ('plasma exchange' or 'immunoabsorption') are used. IRIS is a condition where the recovering immune system can trigger the symptoms of infection. These symptoms can be severe and usually require hospital treatment.

Based on the evaluation of the currently available data and the scientific discussion within the Committee, the CHMP concluded that the benefits of Tysabri continue to outweigh its risks, and therefore recommended that its marketing authorisation be maintained. The Committee noted that the risk-minimisation strategies in place since Tysabri's initial authorisation in the EU have been continuously updated and strengthened to increase awareness of the risk of PML. However, it has now recommended that the following measures also be introduced to make sure that patients and doctors are fully aware of the risk of PML:

- the prescribing information for Tysabri should be updated to reflect the fact that the risk of PML increases after two years of treatment;
- patients should be fully informed about the risk of PML both by their doctor and in an updated 'patient alert card';
- patients should discuss the risks of Tysabri with their doctor both when treatment starts and again after two years. Forms should be available for patients to sign at both time points to show that they have been informed of the risks associated with the medicine. Completed forms will be stored in the patients' medical notes;
- patients who develop signs of PML should have their treatment stopped promptly. These patients should be closely monitored for signs of IRIS, particularly if they have plasma exchange or immunoadsorption. Intensive care facilities should be available in case patients develop severe IRIS.

The Committee also confirmed the existing recommendations that patients, and their carers, partners and families be made aware of the symptoms of PML.

The full changes to the information to doctors and patients are detailed [here](#). The Committee also recommended that regulatory authorities in the EU Member States agree measures to further enhance the monitoring of patients with the company that makes Tysabri. These measures are detailed [here](#).

What are the recommendations for patients and prescribers?

- Patients and prescribers should be aware of the risk of PML with Tysabri, and that this risk increases after two years of treatment.
- Patients, as well as their carers and families, should be aware of the symptoms of PML and report any such symptoms to their doctor urgently.
- Prescribers should follow the recommendations in the updated prescribing information for Tysabri. These include close monitoring of patients before, during and after Tysabri treatment including regular magnetic resonance imaging (MRI) scans, discussing the risks of PML with their patients before treatment, and considering whether treatment should continue beyond two years.
- Patients who have any questions should speak to their doctor.

A European Commission decision on this opinion will be issued in due course.

The full European public assessment report for Tysabri is available [here](#).