August 2008

IMPORTANT SAFETY INFORMATION
Direct Healthcare Professional Communication on the association of natalizumab (TYSABRI) with Progressive Multifocal Leukoencephalopathy (PML)

Dear Health Care Professional,

Summary

- At the end of July 2008, two cases of Progressive Multifocal Leukoencephalopathy (PML) were reported in patients with Multiple Sclerosis (MS) receiving natalizumab (TYSABRI) in the European post-marketing setting.
- In these cases, TYSABRI was given as monotherapy for approximately 17 and 14 months.
- Clinical vigilance by the prescribing physicians to the possibility of PML with TYSABRI was important in identifying these two cases.
- These cases remind healthcare professionals of the importance of:
  - Continued clinical vigilance throughout treatment;
  - Prompt discontinuation of TYSABRI when PML is suspected with subsequent appropriate evaluation, including magnetic resonance imaging (MRI) scan and lumbar puncture.
- The content of this letter has been agreed with the European Authorities, including the Irish Medicines Board (IMB).

Further information on the safety concern

PML is a subacute evolving CNS disease caused by reactivation of JC virus predominantly in immunocompromised patients. PML usually leads to severe disability or death.

There have been a total of four cases of PML in MS patients receiving TYSABRI.

Two cases had been observed in patients receiving TYSABRI in combination with beta-interferon in pre- authorisation clinical trials. Combination therapy is contraindicated in the Summary of Product Characteristics (SmPC). One of these two cases was fatal.

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Company Registration Number 421718

The two cases, reported at the end of July 2008, have been observed post-marketing; TYSABRI was given as monotherapy for approximately 17 and 14 months. In both cases the diagnosis was confirmed on the basis of a combination of clinical signs, symptoms, MRI scan and detection of JC viral DNA in the cerebrospinal fluid (CSF). Both patients have had plasma exchange to remove TYSABRI from circulation and both are being actively followed up.

These cases emphasise the importance of clinical vigilance in the management of patients treated with TYSABRI.

As of June 2008, approximately 31,800 patients with MS worldwide are being treated with TYSABRI. Considering all patients treated with TYSABRI, both in clinical trials and in the post-marketing setting, approximately 13,900 patients have received at least one year of TYSABRI therapy and approximately 6,600 patients have been on therapy for 18 months or longer. The absolute risk of PML in patients treated with TYSABRI cannot be precisely estimated.

Further information on recommendations to healthcare professionals

If a patient develops PML, TYSABRI must be permanently discontinued.

- TYSABRI must be prescribed in strict compliance with the SmPC and according to the Physician Information and Management Guidelines.

- Before initiation of treatment with TYSABRI, a recent MRI should be available. During treatment, patients must be monitored at regular intervals for any new or worsening neurological symptoms or signs that may be suggestive of PML. If new neurological symptoms occur, further dosing is to be suspended until PML has been excluded.

- The clinician should evaluate the patient to determine if the symptoms are indicative of neurological dysfunction, and if so, whether these symptoms are typical of MS or possibly suggestive of PML. If they are suggestive of PML, or if any doubt exists, treatment with TYSABRI should be discontinued and further evaluation, that may include MRI scan, lumbar puncture to test for JC Viral DNA in CSF and repeat neurological assessments, should be conducted. Once the clinician has excluded PML, dosing of TYSABRI can resume.

- TYSABRI is contraindicated in patients with increased risk for opportunistic infections, including immunocompromised patients (including those currently receiving immunosuppressive therapies or those immunocompromised by prior therapies, e.g. mitoxantrone or cyclophosphamide);

Further detailed guidance concerning the management of patients treated with TYSABRI is provided in the Physician Information and Management Guidelines for Multiple Sclerosis patients on TYSABRI.

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Call for reporting

Please remember that any suspected adverse reactions following the use of TYSABRI should be reported to Biogen Idec on 1800 812 719 and/or to the Irish Medicines Board in the usual way.

Communication information

For further information please contact: Medical Information 1800 812 719.

Yours faithfully,

Dr Elias Kouchakji
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