NATIONAL PBM COMMUNICATION
FDA Information for Healthcare Professionals Regarding Natalizumab and PML
August 27, 2008

The Food and Drug Administration (FDA) and the manufacturers of natalizumab (Tysabri®, Biogen-Idec) have reported two additional cases of PML (progressive multifocal leukoencephalopathy). The first case was reported on July 30, 2008 with the second case reported one day later. These were the first reported cases of PML with natalizumab as monotherapy.

Natalizumab was temporarily withdrawn from the market in 2005 because of the occurrence of three cases of PML. PML is a demyelinating disease of the CNS caused by the JC polyoma virus, which is mainly seen in immunocompromised patients. Two of the initial three cases occurred in patients being treated for multiple sclerosis (MS) and the third case of PML occurred in a patient receiving natalizumab for Crohn's disease.[1,2] The reason for developing PML with natalizumab is still unknown. In an extensive evaluation of 3116 patients who had received natalizumab while participating in clinical trials, clinical history and examinations, MRIs, and testing of CSF for JC virus DNA were performed.[3] Based on these evaluations, the investigators found that the estimated incidence of PML associated with exposure to natalizumab (with a mean exposure of 17.9 months) was 1.0 case per 1000 patients (95% CI, 0.2-2.8 per 1000).[4] As of June 2008, there are approximately 31,000 persons that received natalizumab globally and approximately 13,900 that received one year of therapy.

The current FDA report describes two additional cases of PML which have been reported in Europe. One patient had received natalizumab as a first line therapy because of the aggressive nature of his disease, and had been on natalizumab monotherapy for 17 months before developing a slowly progressive focal twitching and weakness in one arm. Brain MRI showed a lesion that was not typical for MS. However, his spinal fluid was negative for JC virus. A subsequent spinal fluid was collected and demonstrated JC virus. He received five courses of plasma exchange and is currently stable and at home. The second patient had received immune-suppressing (azathioprine) and immune-modulating (beta interferon) therapies in the past. At the time of the event he was on natalizumab monotherapy for 14 months before developing PML symptoms (weakness on one side of the body). Despite treatment with steroids his symptoms progressed and included cognitive changes. His new MRI changes were not typical for MS, and spinal fluid was positive for JC virus.

Providers must remain vigilant for symptoms of PML. To ensure close monitoring, all patients must enroll in the "TOUCH Prescribing Program" by completing an enrollment form. All patients must be thoroughly informed of the risks of natalizumab therapy, read and sign a detailed consent form and be enrolled in TOUCH. The patient must be evaluated by an informed health professional before each monthly infusion. Natalizumab should not be given if PML is suspected. The TOUCH program provides guidelines for distinguishing PML from MS including MRI and cerebrospinal fluid assessment for JC virus DNA where PML might be considered.

The report of these two new cases of PML does not alter the presumed risk (1/1000) of developing PML in patients receiving natalizumab. It does demonstrate the need for continued close monitoring and follow up of patients receiving natalizumab. Yearly brain MRI scans, as well as consideration of brain MRI scan for any new or atypical neurological symptoms, are recommended to allow early detection of non-MS type lesions.

Any suspected cases of PML in natalizumab patients must be reported to FDA's MedWatch and VA ADERS program—please consult with local pharmacy staff if such an event occurs.

REFERENCES

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