

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Yousry TA, Major EO, Ryschewitsch C, et al. Evaluation of patients treated with natalizumab for progressive multifocal leukoencephalopathy. *N Engl J Med* 2006;354:924-33.



IMPORTANT DRUG WARNING
VOLUNTARY SUSPENSION OF
TYSABRI[®] (natalizumab) MARKETING

February 28, 2005

Dear Healthcare Professional,

Biogen Idec and Elan Pharmaceuticals are announcing a voluntary suspension in the marketing of TYSABRI, a multiple sclerosis therapy. We are suspending supply of TYSABRI from commercial distribution and physicians should suspend dosing of TYSABRI until further notification. In addition, we have suspended dosing in all clinical trials. These actions, which we believe are in the best interest of patients, have been taken in consultation with FDA. You will be notified regarding the procedure for returning unused product.

This decision is based on reports of two serious adverse events that have occurred in patients treated with TYSABRI in combination with AVONEX[®] (Interferon beta-1a) in clinical trials of multiple sclerosis. These events involve one fatal, confirmed case and one suspected case of progressive multifocal leukoencephalopathy (PML), a rare and frequently fatal demyelinating disease.

We recommend that you evaluate your patients with signs and symptoms of PML and immediately report any potential case to Biogen Idec at 1-888-489-7227. Alternatively, this information may be reported to FDA's MedWatch reporting system by telephone (1-800-FDA-1088), facsimile (1-800-FDA-0178), the MedWatch web site at www.fda.gov/medwatch, or mailed to MedWatch, HF-2, 5600 Fishers Lane, Rockville, MD 20853-9787.

Both patients described in these reports received more than 2 years of TYSABRI therapy (37 and 28 monthly doses) in combination with AVONEX. Neither patient had a known history

of immunosuppression. Both patients presented with progressive neurological deterioration, initially suspected to be worsening of pre-existing multiple sclerosis. Due to the progressive nature of the symptoms and MRI findings atypical for multiple sclerosis, alternate diagnoses were sought, leading to consideration of PML.

In total, approximately 3,000 patients have been treated with TYSABRI in clinical trials of multiple sclerosis, Crohn's disease, and rheumatoid arthritis. The two cases described above are the only reports of PML to date in multiple sclerosis patients treated with natalizumab and AVONEX combination therapy. To date, we have received no reports of PML in multiple sclerosis patients receiving monotherapy with either TYSABRI or AVONEX, nor have we received any reports of PML in patients with Crohn's disease or rheumatoid arthritis in TYSABRI clinical trials.

PML is a rare, progressive, demyelinating disease of the central nervous system that primarily affects immuno-compromised patients. PML is caused by activation of JC virus, a polyomavirus that resides in latent form in up to 80% of healthy adults. The factors leading to activation of the latent infection are not fully understood.

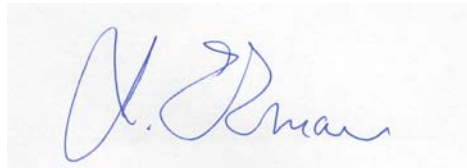
The presenting symptoms of PML typically include impaired cognition, cortical blindness, and hemiparesis. PML lesions are hyperintense on T2-weighted MRI scans and usually do not enhance on T1-weighted scans following gadolinium infusion, unlike new multiple sclerosis lesions, which usually enhance for up to 2 months. Most PML patients have multi-focal lesions of the white matter, although some cases may present with a single new lesion, usually without mass effect.

We are extensively evaluating TYSABRI-treated patients in clinical trials and convening an expert panel to better understand the possible risk of PML in TYSABRI-treated patients. Because we believe in the promising therapeutic benefit of TYSABRI we are working to complete these evaluations quickly. We will use the outcome of these evaluations, in discussion with regulatory authorities, to determine future commercial availability. We will inform you of important new information or developments. If you have further questions or require additional information, please contact Biogen Idec at 1-888-489-7227.

Sincerely,



Burt Adelman, MD
Executive Vice President,
Development
Biogen Idec



Lars Ekman, MD, Ph.D.
Executive Vice President and President
Global Research and Development
Elan Pharmaceuticals