July 2006

# IMPORTANT DRUG WARNING

Dear Healthcare Professional:

Biogen Idec and Elan are writing to inform you of important safety information reflected in recent changes to the labeling for TYSABRI® (natalizumab) as it becomes available as monotherapy for patients with relapsing forms of MS. The changes describe the risk of progressive multifocal leukoencephalopathy (PML), an opportunistic viral infection of the brain that usually leads to death or severe disability.

Two cases of PML were observed in 1869 patients with multiple sclerosis treated for a median of 120 weeks. A third case occurred among 1043 patients with Crohn's disease after the patient received 8 doses. The absolute risk for PML in patients treated with TYSABRI® cannot be precisely estimated, and factors that might increase an individual patient's risk for PML have not been identified. Due to this risk, TYSABRI® is approved only under a restricted distribution program, called the TOUCH™ Prescribing Program. In addition, a Medication Guide has been approved by the Food and Drug Administration and a copy of the Medication Guide is required to be given to patients prior to TYSABRI® being administered.

The following **BOXED WARNING** has been added to the Prescribing Information:

WARNING

TYSABRI® increases the risk of progressive multifocal leukoencephalopathy (PML), an opportunistic viral infection of the brain that usually leads to death or severe disability. Although the cases of PML were limited to patients with recent or concomitant exposure to immunomodulators or immunosuppressants, there were too few cases to rule out the possibility that PML may occur with TYSABRI® monotherapy.

- Because of the risk of PML, TYSABRI® is available only through a special restricted distribution program called the TOUCH™ Prescribing Program. Under the TOUCH™ Prescribing Program, only prescribers, infusion centers, and pharmacies associated with infusion centers registered with the program are able to prescribe, distribute, or infuse the product. In addition, TYSABRI® must be administered only to patients who are enrolled in and meet all the conditions of the TOUCH™ Prescribing Program **(see WARNINGS, Progressive Multifocal Leukoencephalopathy; and WARNINGS, Prescribing, Distribution, and Administration Program for TYSABRI®)**.

- Healthcare professionals should monitor patients on TYSABRI® for any new sign or symptom that may be suggestive of PML. TYSABRI® dosing should be withheld immediately at the first sign or symptom suggestive of PML. For diagnosis, an evaluation that includes a gadolinium-enhanced magnetic resonance imaging (MRI) scan of the brain and, when indicated, cerebrospinal fluid analysis for JC viral DNA are recommended **(see CONTRAINDICATIONS and WARNINGS, Progressive Multifocal Leukoencephalopathy)**.

In addition, the updated Prescribing Information includes the 2-year results of the TYSABRI® clinical trial program. Labeling changes have been made in the **CLINICAL STUDIES, INDICATIONS AND USAGE, CONTRAINDICATIONS, WARNINGS, PRECAUTIONS,** and **ADVERSE REACTIONS** sections of the package insert.

Prescribers should be aware that the immune system effects of TYSABRI® may increase the risk for infections. Concurrent use of antineoplastic, immunosuppressant, or immunomodulating agents may further increase the risk of infections, including PML and other opportunistic infections, over the risk observed with use of TYSABRI® alone. The safety and efficacy of TYSABRI® in combination with antineoplastic, immunosuppressant, or immunomodulating agents have not been established.

We would also like to remind you that TYSABRI® has been associated with hypersensitivity reactions, including serious systemic reactions (e.g., anaphylaxis) which occurred at an incidence of <1%. If a hypersensitivity reaction occurs, discontinue administration of TYSABRI® and initiate appropriate therapy. Patients who experience a hypersensitivity reaction should not be re-treated with TYSABRI®.

TYSABRI® is indicated as monotherapy for the treatment of patients with relapsing forms of multiple sclerosis to delay the accumulation of physical disability and reduce the frequency of clinical exacerbations. The safety and efficacy of TYSABRI® beyond two years are unknown. Because TYSABRI® increases the risk of PML, TYSABRI® is generally recommended for patients who have had an inadequate response to, or are unable to tolerate, alternate multiple sclerosis therapies.

The **CLINICAL STUDIES** section of the prescribing information was revised based on the 2-year results of the TYSABRI® clinical trial program in multiple sclerosis. In the monotherapy study, TYSABRI® (n=627) was shown to reduce the relative risk of sustained increase in disability by 42%, compared with placebo (n=315). Seventeen percent of TYSABRI®-treated patients demonstrated sustained increase in disability as compared with 29% of placebo-treated patients. In this study, TYSABRI® also caused a relative reduction in the annualized relapse rate of 67% to a rate of 0.22 as compared with a rate of 0.67 in the placebo-treated patients.

The TOUCH™ Prescribing Program has been developed in consultation with the FDA. This program represents our commitment to the responsible use of TYSABRI®. The TOUCH™ program seeks to achieve the following:

- Physicians and patients are fully informed about the benefits and risks of TYSABRI® before initiating and while on therapy

- Only appropriate patients are prescribed and infused with TYSABRI®
- Only authorized sites infuse TYSABRI®
- All TYSABRI® prescribing physicians and patients are enrolled into the TYSABRI® registry

Biogen Idec and Elan will continue to provide a range of information and services, including reimbursement research, infusion referral assistance, and infusion center and patient materials.

Healthcare professionals should report any serious adverse events possibly associated with the use of TYSABRI® to Biogen Idec at 1-800-456-2255. This information may also be reported to FDA's MedWatch reporting system by phone (1-800-FDA-1088), FAX (1-800-FDA-0178), via the MedWatch website at www.fda.gov/medwatch, or by mail (using postage paid form) to MedWatch, HF-2, 5600 Fishers Lane, Rockville, MD 20852-9787. Health professionals and consumers should use this form for adverse event/product problem reporting.

The revised full Prescribing Information and Medication Guide for patients are enclosed. Should you have questions regarding the use of TYSABRI® or wish to learn more about the TOUCH™ Prescribing Program for TYSABRI®, call 1-800-456-2255.

Sincerely,

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