

Tysabri® Returns for MS Treatment—under Strict Conditions **Return to Market Unusual, but not Unprecedented**

When a prescription drug is pulled from the U.S. market because of safety concerns, it is unusual for that drug to be re-released. Tysabri® is one of a few drugs that have been pulled from the market due to concerns about serious adverse effects and have later returned to the market. Others include:

- **Thalidomide (Thalomid®):** Used in the 1950s - 1960s as a hypnotic and for relief of morning sickness, thalidomide was discovered to cause severe birth defects. However, the drug has since been granted Orphan Drug status for treatment of several conditions including leprosy, primary brain lesions, Crohn's disease, Kaposi's sarcoma, and mycobacterium infections, among others. Most recently, the FDA approved it this past May for the treatment of newly diagnosed multiple myeloma. The drug is only available through a heavily regulated safety program, the "System for Thalidomide Education and Prescribing Safety" or STEPS.
- **Alosetron (Lotronex™):** First approved in February 2000, 70 cases of severe side effects were reported over the next several months. These included 49 cases of ischemic colitis, some of which required surgery, and at least 3 cases that resulted in death. Alosetron was pulled off the market in November of 2002. It has since been re-released for some severe types of irritable bowel syndrome, but at a lower starting dose. Dispensing pharmacists must follow the rules of the manufacturer's "Prescribing Program for Lotronex" or PPL, and a patient-physician agreement must be signed.
- **Isotretinoin (Accutane®):** Isotretinoin was FDA-approved in May 1982 and is prescribed for treatment of serious dermatologic conditions, among other uses. The drug is teratogenic and causes serious birth defects. In 2001, the SMART Program (System to Manage Accutane Related Teratogenicity) was announced; the program was developed to prevent females who are pregnant from receiving isotretinoin and to prevent pregnancies from occurring while a female is taking isotretinoin. In 2005, the FDA announced a strengthened risk management program called iPLEDGE. Starting March 1, 2006 all prescribers, pharmacies, and patients must be registered in iPLEDGE in order to prescribe, dispense or receive isotretinoin.

Natalizumab (Tysabri®) is a monoclonal antibody specific for leukocytic integrin molecules. It was licensed in November 2004 for the treatment of adults with relapsing forms of multiple sclerosis (MS). At the time, this new drug generated a great deal of hope that MS patients who had failed other therapies would have a new and effective treatment option. However, Biogen Idec and Elan Pharmaceuticals withdrew the drug from the market after only three months when two patients who had received natalizumab during clinical trials later died from progressive multifocal leukoencephalopathy (PML). A third patient was also diagnosed with PML but survived. Clinical trials of the drug were put on hold for a year, to allow time to confirm that no other cases of PML had occurred.

The manufacturers of Tysabri went back to the FDA in 2005, with a proposal that the drug be allowed back on the market with a new risk-management program. The FDA's Peripheral and Central Nervous System Drugs Advisory Committee met in March 2006 and voted to approve the drug under a risk management plan that included mandatory patient and physician registries. The FDA subsequently approved the reintroduction of Tysabri on June 5, 2006 under the strict guidelines of this plan, named "Tysabri Outreach: United Commitment to Health", or TOUCH™. Tysabri may not be used in combination with certain other MS drugs under the new program.



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The TOUCH™ program requires the following:

1. Prescribers must be registered with TOUCH and must agree to comply with the program. The physician must verify that the patient has a relapsing form of MS before prescribing Tysabri and must agree to the patient monitoring requirements.
2. Only infusion centers that are registered and authorized under TOUCH will be able to administer Tysabri. The infusion center may only accept Tysabri orders from prescribers who have registered with TOUCH, and for patients who are enrolled in TOUCH.
3. Only pharmacies registered with TOUCH will be able to purchase and dispense Tysabri; the drug may only be dispensed to authorized infusion centers.
4. Patients must enroll in TOUCH and must agree to the monitoring program, which includes:
 - Patient interview prior to each dose, including verification of patient registration, questions about new or worsening medical problems, and a review of recent and current medications that could increase the risk of adverse effects. The interview sheet is faxed to the drug company within 24 hours of completion.
 - Patient evaluation 3 months after the first infusion, 6 months after the first infusion, and every 6 months thereafter.
 - A confirmed case of PML or other serious opportunistic infection must be reported to the FDA within 15 days
 - The drug company must give the FDA quarterly reports of adverse effects for the first year. Subsequent reports will occur twice a year for 2 years and then annually.

The following is a brief, limited review — please refer to the complete prescribing information before prescribing and/or administering Tysabri to an individual patient.

Indications: Tysabri is indicated as monotherapy for treatment of relapsing MS in adults, to delay the accumulation of physical disability and reduce the frequency of clinical exacerbations. Safety and efficacy beyond 2 years of therapy are unknown. Because of the risk of PML, it is generally only recommended for patients who have had an inadequate response to, or are unable to tolerate, alternate therapies for MS.

Hypersensitivity: There is a possibility of hypersensitivity and/or anaphylactoid reactions. The incidence of such reactions was less than 1% of patients in early clinical trials. The reactions usually occurred within two hours of the start of the infusion. Patients who do experience hypersensitivity to Tysabri should not be given further doses.

Dosing and Administration: The dose is 300 mg IV every 4 weeks, mixed in 100 ml of 0.9% Sodium Chloride and infused over 1 hour. Solutions of the drug must be used within 8 hours of mixing. Patients must be observed during the entire infusion and for at least 1 hour afterwards.

Reporting Adverse Events: All healthcare professionals involved in prescribing, dispensing, and administering Tysabri are requested to report any serious adverse events possibly associated with this drug to Biogen Idec at 1-800-456-2255 immediately. Such events may also be reported to the FDA's MedWatch program at 1-800-FDA-1088 or via the MedWatch website at www.fda.gov/medwatch.

References:

1. Manufacturer's information
2. Clinical Pharmacology [database online], Tampa FL: Gold Standard, Inc.; 2006. URL: <http://cp.gsm.com>. Accessed 9/15/06.
3. Traynor K. Tysabri's return draws cautious optimism. Am J Health-Syst Pharm. 2006; 63:1388.



Patients must be asked about their symptoms and medications before each dose of Tysabri

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All adverse reactions to Tysabri must be reported and reviewed