



National Multiple Sclerosis Society
733 Third Avenue
New York, New York 10017-3288
Tel +1 212.986.3240
Fax +1 212.986.7981
E-mail nat@nmss.org
nationalmssociety.org

RESEARCH/CLINICAL UPDATE

Updated February 1, 2008

TYSABRI: FREQUENTLY ASKED QUESTIONS AND THEIR ANSWERS

Introduction: Following the June 2006 FDA approval of Tysabri[®] (natalizumab, Biogen Idec and Elan Pharmaceuticals) for relapsing multiple sclerosis, in July Biogen Idec and Elan Pharmaceuticals commercially launched the drug in the U.S. The drug, given by monthly I.V. infusion, is only available to patients and prescribing physicians who have registered in the TOUCH[™] Prescribing Program, and infusions are only available at registered infusion sites where medical personnel have been trained in Tysabri's use and in the risks of PML. PML (progressive multifocal leukoencephalopathy) is a brain disease that occurred in three people (two of whom died) who had been in clinical trials of Tysabri.

ABOUT TYSABRI

Q. What is Tysabri (pronounced Tie-SAB-bree) and how does it work?

A. Tysabri (whose scientific name is natalizumab, pronounced: nat-tal-IZ-zue-mab) is a laboratory-produced monoclonal antibody. Tysabri works differently than other MS medicines. It is available in the U.S. for relapsing forms of MS, based on data from the first year of two, 2-year clinical trials.

Although Tysabri's exact method of action is not fully understood, one of the ways that it may work against MS is by blocking the binding of alpha 4 integrins to vascular cell adhesion molecules (VCAM-1s). That effectively prevents white blood cells from crossing the blood-brain barrier. Tysabri may also have additional effects within the brain and central nervous system, helping to block other processes that increase inflammation and lead to nerve damage. Based on these possible mechanism of action, studies have shown that Tysabri works to reduce relapses and worsening of disability.

This approach was initially studied in animal models, including studies supported by the National MS Society, which showed that monoclonal antibodies could block such immune cell movement and ameliorate disease. These animal studies led to the successful human studies.

Q. How many patients and physicians are using Tysabri?

A. As of late December 2007:

- In the US, approximately 12,900 patients are on Tysabri commercially and about 2,500 physicians have prescribed the therapy
- In the EU, approximately 7,500 patients are on Tysabri therapy commercially; and
- In global clinical trials, approximately 1,000 patients are on Tysabri therapy

(To date, no new cases of PML have been confirmed.)

Q. Who should take Tysabri?

A. Tysabri has been approved for persons with relapsing forms of multiple sclerosis.

Relapsing MS means that individuals experience flare-ups of symptoms in the form of periodic attacks, which then subside with total or partial recovery. Relapsing forms of MS may include those with relapsing-remitting MS, progressive-relapsing MS, and those with secondary-progressive MS who experience relapses.

Because of the chance for PML, Tysabri is generally recommended for patients that have not been helped enough by, or cannot tolerate other treatments for MS.

Q. In terms of who can be prescribed Tysabri, who determines what constitutes an “inadequate response” to currently approved MS therapies?

A. The FDA’s approval of Tysabri does not specifically define “inadequate response,” nor does it define what constitutes an inability to tolerate alternate MS therapies. Therefore, the decision about whether to start or switch to Tysabri must be made after careful consideration by a person with MS together with his or her personal physician.

Q. Where will I have to go to get Tysabri infusions?

A. After the physician determines that the patient is an appropriate candidate for treatment with Tysabri, and after discussing the potential risks and benefits of taking the drug, the patient and prescriber complete the enrollment forms for the TOUCH Prescribing Program.

According to company sources, after the enrollment forms are received, the patient will be assigned a case manager who will help locate the most convenient authorized infusion site.

Q. How much does Tysabri cost?

A. The wholesale price of Tysabri has been set at \$2184.62 per vial. It is administered 13 times per year, for an annual wholesale cost of \$28,400. (There will be additional costs for infusion services, which will range widely depending on the setting and region of the country.)

According to Elan’s site (www.elan.com), “Elan and Biogen Idec are committed to making Tysabri accessible to appropriate patients who may benefit from therapy. To achieve this goal, programs have been developed to assist patients who are uninsured or who require financial assistance. Patients who require financial assistance can receive more information by calling MS ActiveSource at 1-800-456-2255.”

The Society will work closely with the companies to ensure that they pursue their commitment of providing access for those people with MS for whom this treatment may be appropriate.

Q. Will my insurance cover the cost of Tysabri?

A. Insurance coverage for Tysabri will vary based on an individual's plan. The actual price you pay may vary based on your health plan coverage, as well as where you receive Tysabri. For patients enrolled in the TOUCH Prescribing Program, Biogen Idec can provide assistance in researching insurance coverage for Tysabri. Some may be uninsured and require assistance to access Tysabri. To learn more about financial assistance options call MSActiveSource at 1-800-456-2255.

Q. Does Medicare cover the use of Tysabri?

A. Tysabri is covered under Medicare Part B, but is not covered under Medicare Part D.

Q. How is Tysabri administered? Is Tysabri a pill or a shot (injection)?

A. Tysabri is taken differently than other MS medicines. Tysabri is not a pill or an injection. Instead, Tysabri is infused into a vein once every 4 weeks.

Q. What should I expect at the infusion? Does it hurt? How long does it take to receive an infusion of Tysabri?

A. To receive your dose, you make an appointment at your authorized infusion center and visit once every 4 weeks. The nurse will ask you a series of questions about how you are doing and complete a Pre-infusion Patient Checklist. Each Tysabri infusion will take about 2 hours, although your visit may last longer. When you're ready to receive the dose, a nurse will prepare an IV line into your arm and connect the line to your Tysabri drip bag. There will be a quick stick from the needle, but it shouldn't hurt otherwise. Then you can sit comfortably while the dose enters your bloodstream over the course of an hour. After your infusion, you will need to remain at the center for another hour where you will be observed to make sure there are no side effects.

Q. Where do I get my infusion?

A. The infusion will need to take place at an infusion center that is authorized by the TOUCH Prescribing Program. Often infusion centers are located in the same hospital or clinic where you meet with your doctor. Your TOUCH Case Manager and your healthcare team can help you find an infusion site near you. For more information, call MSActiveSource at 1-800-456-2255.

Q. Should I switch from the therapy I'm taking now?

A. This question can only be answered through discussions between an individual and his or her neurologist. The discussion should focus on how well the individual is doing on his or her current therapy and what is currently understood about the potential risks and benefits of Tysabri.

Q. I have relapsing MS and have never tried any of the disease-modifying therapies. Will I be able to use Tysabri?

A. This is a question you should discuss with a neurologist who is knowledgeable about MS and familiar with your condition and personal circumstances. The FDA's approval states that Tysabri is generally recommended for patients who have had inadequate response to other approved MS therapies, the U.S. label does not preclude using Tysabri as a first line therapy in clinically appropriate situations.

Q. Can I switch to Tysabri if I'm on another MS drug right now?

A. Possibly. This is a matter that should be discussed with your neurologist. The prescribing information states that Tysabri should not be given to patients whose immune systems are compromised, or weakened. There will likely be a period of time between the end of your current therapy and the beginning of Tysabri. The length of time may vary depending on the type of therapy you are currently on and the period necessary to "wash out" the current drug from your system. If a person is currently using an approved MS therapy such as Copaxone or interferon beta and is being switched to Tysabri, the "wash out" period would probably be a few weeks before beginning Tysabri infusions. If a person has recently been prescribed Novantrone, Cytoxan, Imuran or other strong immune-suppressing drug, the "wash out" period would be longer before beginning Tysabri. The FDA-approved prescribing information does not provide specific recommendations for "wash-out" or waiting periods before beginning treatment with Tysabri. Your doctor will decide whether any washout is clinically appropriate for you.

Q. How effective is Tysabri?

A. In a two-year clinical trial of two years' duration (the AFFIRM study) of Tysabri alone, 942 individuals received either Tysabri or inactive placebo for more than two years. The treated group experienced a 42% reduced risk of progression of disability, a 67% reduction of clinical relapses, and an 83% reduction in the development of new or newly enlarging MRI-detected brain lesions. Tysabri also reduced the mean number of enhancing (active) MRI lesions by 92% after the first and second year. These results were described in a published paper ([The New England Journal of Medicine](#) 2006;354:899-910).

A second two-year trial of two years' duration (the SENTINEL study) involved 1171 individuals with relapsing MS who were on Avonex but had experienced at least one relapse during the previous 12 months. All participants continued on Avonex, in combination with

either Tysabri or inactive placebo given by intravenous infusions every four weeks for up to 116 weeks. After one year, participants who had Tysabri added to Avonex experienced a 54 percent reduction in the rate of clinical relapses compared to those on placebo and Avonex, which was also maintained at two years with a 55 percent reduction.

This combination therapy resulted in a 24 percent decrease in the risk of sustained disability progression. MRI scans showed an 83-percent reduction in the Tysabri plus Avonex group in enlarging MRI lesions, and an 89-percent reduction in lesions showing active inflammation. Results of this study were described in a published paper (The New England Journal of Medicine 2006;354:911-923). Two cases of PML, one of which was fatal, were diagnosed in those on combination therapy.

Later published data from clinical trials of Tysabri suggested that this drug significantly improved health-related quality of life (Annals of Neurology 2007;62:335-346) and reduced vision loss (Neurology 2007;68:1299-1304).

Q. What is meant by the statement that Tysabri should not be taken by patients who have compromised immune systems or who are taking other immunosuppressive or immunomodulatory agents?

A. This means that Tysabri would not be used in patients whose immune systems are weak, such as people who have MS and leukemia or lymphoma, or who are taking immune-suppressing drugs or other MS drugs such as interferons (Avonex, Betaseron, Rebif), Copaxone or Novantrone. Other drugs sometimes taken by people with MS which may weaken their immune systems include Cytosan or Imuran, or monthly intravenous steroids.

There is no warning against the use of periodic steroids to treat relapses in people taking Tysabri; however, the chronic use of “pulse” or monthly steroids would possibly weaken the immune system and therefore should probably be avoided.

Q. Is Tysabri better than the other available MS therapies?

A. Tysabri has not been compared head-to-head against any other approved MS drug, and that is the only way to truly compare the effectiveness of the MS drugs. However, generally clinicians agree that the immunomodulatory drugs approved for use in MS reduce the rate of relapses by about one-third. By contrast, after two years Tysabri reduced the rate of relapses by about two-thirds as compared to placebo. The investigators also reported that Tysabri reduced the risk of sustained progression of disability over those two years. There is some evidence that other approved MS drugs also slow disease progression.

It is important to note that since MS is such a diverse disease, there is no “one size fits all” treatment strategy. Any decision about whether to take any of the disease-modifying therapies should be made after careful discussion between a patient and his or her physician of its potential risks and benefits. The National MS Society does recommend that upon diagnosis

individuals with relapsing MS consider early proactive treatment with one of the FDA-approved [therapies for MS](#) that have been shown to impact the underlying disease course.

Q. Where can I get more information about Tysabri?

Additional information is available at the following resources:

- ✓ For a summary of the TOUCH risk management program:
<http://www.fda.gov/cder/drug/infopage/natalizumab/RiskMAP.pdf>
- ✓ For patient-oriented medication guide (in PDF format): <http://www.Tysabri.com/Tysabri-medguide.pdf>
- ✓ For physician-oriented prescribing information:
<http://www.Tysabri.com/product-information.html>
- ✓ For information from the FDA about Tysabri, go to the FDA's Web site at:
<http://www.fda.gov/cder/drug/infopage/natalizumab/default.htm>
- ✓ If you'd like to receive a Tysabri patient brochure or need more information about Tysabri, MSActiveSource at 1-800-456-2255, or go to the Biogen Idec's Tysabri site at <http://www.Tysabri.com>.

SAFETY CONCERNS ABOUT TYSABRI

Q. What is the primary safety concern regarding the use of Tysabri?

A. A primary safety issue is the increased risk of PML. Three people who had been in clinical trials involving Tysabri developed a rare disease called PML (progressive multifocal leukoencephalopathy), caused by a common virus called the JC virus. Two of them died. The two MS patients who developed PML were taking Tysabri and Avonex at the same time.

There were some 'suspected cases' reported by the media. However, a thorough evaluation of about 3000 Tysabri-treated patients from clinical trial, overseen by an independent committee of PML experts, found no additional confirmed cases of PML. In clinical trials, two cases out of 1869 MS patients who had taken Tysabri were found, and one case out of 1043 Crohn's Disease patients. **No new cases of confirmed PML have been reported since Tysabri has been on the market.**

Q. If I take Tysabri, what are the risks that I will get PML?

A. No one knows the true risk of getting PML outside of the clinical trials of people taking Tysabri. According to a study published in The New England Journal of Medicine ([The New England Journal of Medicine 2006;354:924-33](#)), the risk in the clinical trials population, who had taken an average of 17.9 doses of Tysabri, is one in one thousand.

There is not enough known about the true risk of getting PML in people who may use Tysabri. For these and other reasons, Biogen Idec and Elan have developed procedures for the careful

tracking of adverse events and has established a large observational study to help evaluate the long-term safety of Tysabri.

Q. Will I be safe if I take Tysabri alone, without any other drugs that alter the immune system?

A. No one knows. During the March 2006 advisory committee meeting held by the FDA about Tysabri, FDA representatives stated that the risk of PML in those who took Tysabri alone versus those who took Tysabri in combination with Avonex is still unclear. That means that at this time there is insufficient data to determine whether PML was caused by taking Tysabri in combination with other immune-modulating drugs, or whether PML can arise in those taking Tysabri alone.

Q. How will safety be monitored? What is a RiskMAP?

Risk Minimization Action Plans, or RiskMAPs, are programs that the FDA has started to implement with increasing frequency “to meet specific goals and objectives in minimizing known risks of a product while preserving its benefits.” Other medications that utilize a RiskMAP to facilitate appropriate use include Clozaril[®] (clozapine), Accutane[®] (isotretinoin), Lotronex[®] (alosectron hydrochloride), and Novantrone[®] (mitoxantrone). In 2005, the FDA issued guidance telling manufacturers how to structure these types of programs.

Q. What is the TOUCH Prescribing Program?

TOUCH (Tysabri Outreach: Unified Commitment to Health) was developed in conjunction with the FDA to facilitate the appropriate use of Tysabri and to assess, on an ongoing basis, the incidence and risk factors for PML and other serious opportunistic infections associated with Tysabri treatment.

In order to receive Tysabri, patients must:

- Talk to their doctors and understand the benefits and risks of Tysabri
- Agree to follow all of the instructions in the TOUCH Prescribing Program
- Sign the Prescriber/Patient Enrollment Form

Tysabri can only be:

- Prescribed by doctors who are enrolled in the TOUCH Prescribing Program
- Infused at infusion centers that are enrolled in the TOUCH Prescribing Program
- Given to patients who are enrolled in the program

Patients should plan to see their doctors 3 months after the first infusion, then again 6 months after the first infusion, and at least every 6 months thereafter.

Q. Are there any tests that can be done to know in advance whether you are at risk for developing PML?

A. No.

Q. Are there any tests that can be done to know if you are developing PML?

A. Yes. If a person begins to show persistent signs of new or worsening neurological symptoms, they would likely be taken off Tysabri. Then their doctor would likely begin tests of the blood and spinal fluid as well as obtain an MRI scan of the brain to help determine whether the JC virus that causes PML is present and active.

Q. What are the signs of PML that a person using Tysabri should look out for?

A. All of this will be clearly explained in patient information that will be supplied to individuals before they begin taking Tysabri. Patients will be cautioned to inform their prescribing physicians and/or infusion nurse if they experience any new or worsening neurological symptoms. These might include any changes in thinking, eyesight, balance, strength and other symptoms.

Q. What is the treatment for PML?

A. There is at present no drug that has been proven to fight the JC virus. Therefore, treatment consists of reconstituting the immune system by withdrawing any immune-suppressing therapies.

Q. Are there risks of getting other serious infections if I take Tysabri?

A. The clinical trials of Tysabri in MS did not reveal significant differences in serious infections between those on active treatment versus those on inactive placebo. However, the risks of longer-term exposure to Tysabri are currently unknown.

FDA scientists reviewing safety data pointed out that Tysabri's mode of action inhibits the recruitment of immune cells to sites of infection, making it possible that risks of serious or opportunistic infection may exist. According to the drug's labeling, the immune system effects of Tysabri may increase the risk for infections. During clinical trials, certain infections occurred more often in those taking Tysabri, including pneumonias, urinary tract infections, gastroenteritis, vaginal infections, tooth infections, tonsillitis and herpes infections.

Q. I read that the FDA has included a “Black Box Warning” on Tysabri’s label. What does that mean?

A. According to the FDA, a Black Box Warning is “ the most serious warning placed in the labeling of a prescription medication... Black box warnings are designed to highlight special problems, particularly those that are serious, and to give health care professionals a clear understanding of a potential medical complication associated with a drug. Black box warnings provide physicians with important insights as to how to prescribe a drug that may be associated with serious side effects in a way that maximizes its benefits and minimizes its risks.”

The Black Box Warning for Tysabri warns of the increased risk of PML and the importance of monitoring patients using the drug for any new sign or symptoms that may be suggestive of PML.

Q. Are any other side effects possible if I'm taking Tysabri?

A. Yes. These will be detailed in the patient materials prepared by the drug's sponsors. In a two-year clinical trial of Tysabri alone, some of the adverse events reported significantly more frequently in those on Tysabri included fatigue, allergic reaction, and hypersensitivity reactions. In a two-year clinical trial of Tysabri in combination with Avonex, adverse events experienced significantly more often in those on combination therapy included anxiety, sore throat, sinus congestion and peripheral edema (swelling). In addition, two cases of PML, one of which was fatal, were diagnosed in those on combination therapy. For more information, go to www.Tysabri.com.

NATIONAL MS SOCIETY'S ROLE IN ADVANCING NEW TREATMENTS

Q. What has the National MS Society done to advance the development of new drugs, including Tysabri?

A. Since the Society's founding in 1946, it has expended over \$600 million to advance MS research, and has been at the core of virtually every major breakthrough in treating and understanding MS.

Over the past 20 years, the National MS Society has invested over \$13 million in 61 clinical studies of potential MS therapies. These investments in basic and applied MS research have made possible significant advancements towards finding effective treatments and improving diagnosis, rehabilitation, and symptomatic therapy for people with all forms of MS, as well as bringing us closer to a cure. For example, it was the Society who began funding the initial research into interferons and glatiramer acetate which led to the development of the current disease modifying medications Avonex, Betaseron, Copaxone, Rebif, and Novantrone -- the first therapies shown to affect underlying disease course.

Q. Was the Society involved in the discovery of Tysabri?

A. Yes. The significance of the integrin molecule, the study of which led to the development of Tysabri, was discovered as part of a Society-funded research fellowship.

Q. What will the National MS Society do if additional people die or experience serious side effects after taking Tysabri?

A. The use of Tysabri carries with it the risk of developing PML, an often fatal disease, and its use for extended periods of time carries unknown risks. If there are new cases, the National MS Society will monitor the situation and disseminate the information. If the risk for PML or other serious adverse events were to significantly rise in clinical use, we would advocate that the FDA take immediate and appropriate action.

Tysabri is a registered trademark of Biogen Idec and Elan.