

Overview

Please see accompanying full Prescribing Information, including Boxed Warning, as well as Important Safety Information on pages 6-9.

TYSABRI[®]
(natalizumab)

INDICATIONS AND USAGE

Multiple Sclerosis (MS)

- TYSABRI (natalizumab) is indicated as monotherapy for the treatment of patients with relapsing forms of multiple sclerosis. TYSABRI increases the risk of PML. When initiating and continuing treatment with TYSABRI, physicians should consider whether the expected benefit of TYSABRI is sufficient to offset this risk. See Full Prescribing Information regarding the risk of PML with TYSABRI

Crohn's Disease (CD)

- TYSABRI is indicated for inducing and maintaining clinical response and remission in adult patients with moderately to severely active Crohn's disease (CD) with evidence of inflammation who have had an inadequate response to, or are unable to tolerate, conventional CD therapies and inhibitors of TNF α . TYSABRI should not be used in combination with immunosuppressants (e.g., 6 mercaptopurine, azathioprine, cyclosporine or methotrexate) or inhibitors of TNF α

Why the program was developed

Biogen Idec is committed to patient safety. The TOUCH Prescribing Program was designed:

- To inform prescribers, infusion center healthcare providers, and patients about the risk of progressive multifocal leukoencephalopathy (PML) associated with TYSABRI including the increased risk of PML with longer treatment duration, prior immunosuppressant use, and the presence of anti JCV antibodies
- To warn against concurrent use with antineoplastic, immunosuppressant, or immunomodulating agents and in patients who are immunocompromised
- To promote early diagnosis of PML and timely discontinuation of TYSABRI in the event of suspected PML

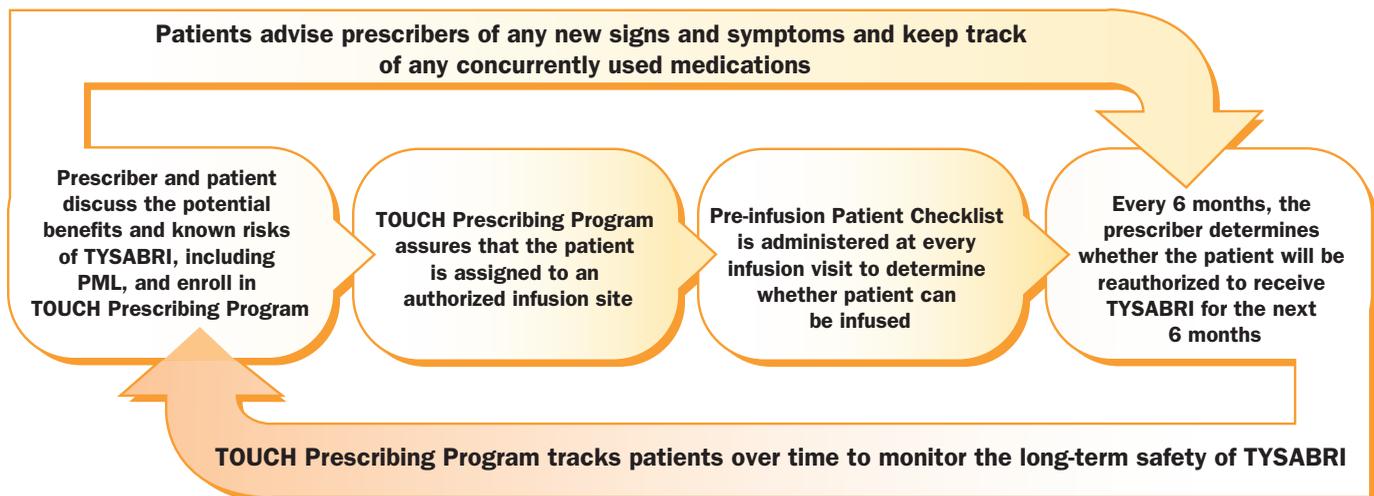
Prescribers, infusion sites, certified pharmacies associated with infusion sites, and patients must all enroll in the TOUCH Prescribing Program in order to prescribe, infuse, dispense, or receive TYSABRI. All completed Enrollment Forms must be faxed to Biogen Idec at 1 800 840 1278.

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- TOUCH On Line is a web based tool designed to:
 - Provide real time access to TYSABRI patient data
 - Maintain compliance with the TOUCH Prescribing program
 - Reduce administrative burden/paperwork for Prescribers and Infusion Sites
- TOUCH On Line is accessed with secure user name and password

How the program works



This Overview serves only as an introduction to the program. For additional details please see the full Prescribing Information, or call 1 800 456 2255.

Compliance with the requirements of the TOUCH Prescribing Program is necessary to maintain authorization to prescribe, dispense, infuse, or receive TYSABRI. Failure to comply with these requirements may result in de-enrollment from the TOUCH Prescribing Program and termination of such authorization.

For more information on the TOUCH Prescribing Program or to obtain additional copies of material, please contact your Biogen Idec representative or call 1 800 456 2255, 8:30 AM to 8:00 PM (ET). The Patient Medication Guide is also available online at www.TYSABRI.com.



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Enrollment

All participants must enroll in the TOUCH Prescribing Program by completing an Enrollment Form.

Prescribers and Patients

Prior to enrollment, prescribers must receive and review the full Prescribing Information and educational materials relating to the TOUCH Prescribing Program. Before completing and signing a Prescriber/Patient Enrollment Form, prescribers and patients are required to:

- Understand and discuss the benefits and risks of treatment with TYSABRI, including PML and other opportunistic infections
- Understand and acknowledge their respective program responsibilities as outlined in the Enrollment Kit

Patients should be fully counseled by either the enrolled prescriber or a healthcare provider under that prescriber's direction before an initial prescription is written. A copy of the completed Prescriber/Patient Enrollment Form should be retained in the patient's medical record. Upon receipt of a properly completed Enrollment Form:

- A Patient Enrollment Number will be assigned
- A Biogen Idec Case Manager will be assigned to assure that the patient is assigned to an authorized infusion site

Infusion Sites and Certified Pharmacies*

Before completing and signing their respective Enrollment Forms, infusion sites and associated certified pharmacies must receive training from a Biogen Idec representative.

*A certified pharmacy is a pharmacy that is part of a hospital, group practice, or infusion site, and is affiliated with one or more infusion sites. Retail pharmacies, wholesalers, and specialty distributors are excluded from holding inventory and dispensing TYSABRI.

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Infusion

Only infusion sites authorized by the TOUCH Prescribing Program can infuse TYSABRI. They are required to:

- Confirm that the patient is currently authorized to receive TYSABRI
- Provide the patient with a copy of the TYSABRI Patient Medication Guide prior to each infusion
- Administer the Pre Infusion Patient Checklist to every patient prior to each infusion and submit it to Biogen Idec within 1 business day, regardless of whether the patient is infused or not

Authorized infusion sites must use the Authorization Number that is provided upon enrollment to order and receive shipments of TYSABRI.* Certified pharmacies may only dispense TYSABRI to authorized, associated infusion sites.

*The TOUCH Prescribing Program utilizes a closed distribution system that restricts all product shipments. This system includes a single distributor, specialty pharmacies under contract with Biogen Idec and authorized certified pharmacies associated with authorized infusion sites.

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Tracking

The TOUCH Prescribing Program will track all patients over time so that Biogen Idec can inform the FDA, prescribers, and patients in a timely manner of information regarding the safety of TYSABRI. Prescribers are required to report any case of PML, serious opportunistic infection, or death in TYSABRI treated patients to Biogen Idec or the FDA. Furthermore, prescribers are also required to cooperate in the investigation of potential adverse events including providing relevant information upon request. The primary tracking tools include:

- Pre infusion Patient Checklist
- Patient Status Report and Reauthorization Questionnaire
- Initial and 6 month Discontinuation Questionnaires

Missing or incomplete forms will prompt TOUCH Case Managers to follow up with infusion sites, patients, and/or prescribers to obtain such information in compliance with program requirements. Prescribers, infusion sites, and certified pharmacies may be audited by the FDA, Biogen Idec, and/or a third party authorized by Biogen Idec.

IMPORTANT SAFETY INFORMATION

Indication

TYSABRI (natalizumab) is indicated as monotherapy for the treatment of patients with relapsing forms of multiple sclerosis. TYSABRI increases the risk of PML. When initiating and continuing treatment with TYSABRI, physicians should consider whether the expected benefit of TYSABRI is sufficient to offset this risk. See important information regarding the risk of PML with TYSABRI.

WARNING

TYSABRI (natalizumab) increases the risk of PML, an opportunistic viral infection of the brain that usually leads to death or severe disability. Risk factors for the development of PML include duration of therapy, prior use of immunosuppressants, and presence of anti-JCV antibodies. These factors should be considered in the context of expected benefit when initiating and continuing treatment with 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 including a gadolinium-enhanced MRI scan of the brain and, when indicated, cerebrospinal fluid analysis for JC viral DNA are recommended.

Because of the risk of PML, TYSABRI is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the TOUCH Prescribing Program.

Progressive Multifocal Leukoencephalopathy (PML)

- Infection by the JC Virus is required for the development of PML.
- Anti JCV antibody testing should not be used to diagnose PML.
- There are no known interventions that can reliably prevent PML or that can adequately treat PML if it occurs. It is not known whether early detection of PML and discontinuation of TYSABRI will mitigate the disease.
- PML has been reported following discontinuation of TYSABRI in patients who did not have findings suggestive of PML at the time of discontinuation. Patients should continue to be monitored for any new signs or symptoms that may be suggestive of PML for approximately six months following discontinuation of TYSABRI.
- In MS patients, an MRI scan should be obtained prior to initiating therapy with TYSABRI. This MRI may be helpful in differentiating subsequent multiple sclerosis symptoms from PML.
- Three sessions of plasma exchange over 5 to 8 days were shown to accelerate TYSABRI clearance in a study of 12 patients with MS who did not have PML, although in the majority of patients, alpha 4 integrin receptor binding remained high. Adverse events which may occur during plasma exchange include clearance of other medications and volume shifts, which have the potential to lead to hypotension or pulmonary edema. Although plasma exchange has not been studied in TYSABRI treated patients with PML, it has been used in such patients in the postmarketing setting to remove TYSABRI more quickly from the circulation.
- Anti JCV antibody testing should not be performed during or for at least two weeks following plasma exchange due to the removal of antibodies from the serum.

Please see accompanying full Prescribing Information, including Boxed Warning.



- Immune reconstitution inflammatory syndrome (IRIS) has been reported in the majority of TYSABRI treated patients who developed PML and subsequently discontinued TYSABRI. In almost all cases, IRIS occurred after plasma exchange was used to eliminate circulating TYSABRI. It presents as a clinical decline in the patient's condition after TYSABRI removal (and in some cases after apparent clinical improvement) that may be rapid, can lead to serious neurological complications or death and is often associated with characteristic changes in the MRI. TYSABRI has not been associated with IRIS in patients discontinuing treatment with TYSABRI for reasons unrelated to PML. In TYSABRI treated patients with PML, IRIS has been reported within days to several weeks after plasma exchange. Monitoring for development of IRIS and appropriate treatment of the associated inflammation should be undertaken.

Contraindications

- TYSABRI is contraindicated in patients who have or have had PML.
- TYSABRI is contraindicated in patients who have had a hypersensitivity reaction to TYSABRI.

TYSABRI TOUCH Prescribing Program

- TYSABRI is available only through a restricted program under a REMS called the TOUCH® Prescribing Program because of the risk of PML.
- For prescribers and patients, the TOUCH® Prescribing Program has two components: MS TOUCH® (for patients with multiple sclerosis) and CD TOUCH® (for patients with Crohn's disease).
- Prescribers must be certified and comply with the following:
 - Review the TOUCH Prescribing Program prescriber educational materials, including the full prescribing information.
 - Educate patients on the benefits and risks of treatment with TYSABRI, ensure that patients receive the Medication Guide, and encourage them to ask questions.
 - Review, complete, and sign the Patient Prescriber Enrollment Form.
 - Evaluate patients three months after the first infusion, six months after the first infusion, every six months thereafter, and for at least six months after discontinuing TYSABRI.
 - Determine every six months whether patients should continue on treatment, and if so, authorize treatment for another six months.
 - Submit to Biogen Idec the "TYSABRI Patient Status Report and Reauthorization Questionnaire" six months after initiating treatment and every six months thereafter.
 - Complete an "Initial Discontinuation Questionnaire" when TYSABRI is discontinued and a "6 Month Discontinuation Questionnaire," following discontinuation of TYSABRI.
 - Report cases of PML, hospitalizations due to opportunistic infections, and deaths to Biogen Idec at 1 800 456 2255 and to the Food and Drug Administration's MedWatch Program at 1 800 FDA 1088 as soon as possible.
- Patients must be enrolled in the TOUCH Prescribing Program, read the Medication Guide, understand the risks associated with TYSABRI, and complete and sign the Patient Prescriber Enrollment Form.
- Pharmacies and infusion centers must be specially certified to dispense or infuse TYSABRI.



Herpes Encephalitis and Meningitis

- TYSABRI increases the risk of developing encephalitis and meningitis caused by herpes simplex and varicella zoster viruses.
- Serious, life threatening, and sometimes fatal cases have been reported in the postmarketing setting in multiple sclerosis patients receiving TYSABRI.
- Monitor patients receiving TYSABRI for signs and symptoms of meningitis and encephalitis. If herpes encephalitis or meningitis occurs, TYSABRI should be discontinued, and appropriate treatment for herpes encephalitis/meningitis should be administered.

Hepatotoxicity

- Clinically significant liver injury, including acute liver failure requiring transplant, has been reported in patients treated with TYSABRI in the postmarketing setting. In some patients, liver injury recurred upon rechallenge, providing evidence that TYSABRI caused the injury.
- Signs of liver injury, including markedly elevated serum hepatic enzymes and elevated total bilirubin, occurred as early as 6 days after the first dose; and signs of liver injury have also been reported for the first time after multiple doses.
- In some patients, liver injury recurred upon rechallenge, providing evidence that TYSABRI caused the injury.
- The combination of transaminase elevations and elevated bilirubin without evidence of obstruction is generally recognized as an important predictor of severe liver injury that may lead to death or the need for a liver transplant in some patients.
- TYSABRI should be discontinued in patients with jaundice or other evidence of significant liver injury (e.g., laboratory evidence).

Hypersensitivity/Antibody Formation

- Hypersensitivity reactions have occurred in patients receiving TYSABRI, including serious systemic reactions (e.g., anaphylaxis), which occurred at an incidence of <1%.
- Reactions usually occur within 2 hours of the start of the infusion. Symptoms associated with these reactions can include urticaria, dizziness, fever, rash, rigors, pruritus, nausea, flushing, hypotension, dyspnea, and chest pain. Generally, these reactions are associated with antibodies to TYSABRI.
- 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.
- Hypersensitivity reactions were more frequent in patients with antibodies to TYSABRI compared with patients who did not develop antibodies to TYSABRI in both MS and CD studies.
- Patients who receive TYSABRI after an extended period without treatment may be at higher risk of hypersensitivity reactions.

Immunosuppression/Infections

- The immune system effects of TYSABRI may increase the risk for infections.

Please see accompanying full Prescribing Information, including Boxed Warning.



- In Study MS1, certain types of infections, including pneumonias and urinary tract infections (including serious cases), gastroenteritis, vaginal infections, tooth infections, tonsillitis, and herpes infections, occurred more often in TYSABRI treated patients than in placebo treated patients. One opportunistic infection, a cryptosporidial gastroenteritis with a prolonged course, was observed in a patient who received TYSABRI in Study MS1.
- In Studies MS1 and MS2, an increase in infections was seen in patients concurrently receiving short courses of corticosteroids. However, the increase in infections in TYSABRI treated patients who received steroids was similar to the increase in placebo treated patients who received steroids.
- Concurrent use of antineoplastic, immunosuppressant, or immunomodulating agents may further increase the risk of 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.
- In Study MS1 and Study MS2, the rate of any type of infection was approximately 1.5 per patient year in both TYSABRI treated patients and placebo treated patients.
- In Study MS1, the incidence of serious infections was approximately 3% in TYSABRI treated patients and in placebo treated patients. Most patients did not interrupt treatment with TYSABRI during infections.
- In postmarketing experience, serious herpes infections have occurred.

Laboratory Test Abnormalities

- In clinical trials, TYSABRI was observed to induce increases in circulating lymphocytes, monocytes, eosinophils, basophils, and nucleated red blood cells. Observed changes persisted during TYSABRI exposure, but were reversible, returning to baseline levels usually within 16 weeks after the last dose. Elevations of neutrophils were not observed. TYSABRI induces mild decreases in hemoglobin levels that are frequently transient.

Adverse Reactions

- The most common adverse reactions reported at an incidence of $\geq 10\%$ with TYSABRI and $\geq 2\%$ difference with placebo were headache (38% vs 33%), fatigue (27% vs 21%), infusion reactions (24% vs 18%), urinary tract infections (21% vs 17%), arthralgia (19% vs 14%), depression (19% vs 16%), pain in extremity (16% vs 14%), rash (12% vs 9%), gastroenteritis (11% vs 9%), and vaginitis* (10% vs 6%).

*Percentage based on female patients only.

- The most frequently reported serious adverse reactions in Study MS1 were infections (3.2% vs 2.6% placebo), including urinary tract infection (0.8% versus 0.3%) and pneumonia (0.6% versus 0%), acute hypersensitivity reactions (1.1% vs 0.3%, including anaphylaxis/anaphylactoid reaction [0.8% versus 0%]), depression (1.0% vs 1.0%, including suicidal ideation or attempt [0.6% versus 0.3%]), and cholelithiasis (1.0% vs 0.3%).
- Based on animal data, TYSABRI may cause fetal harm. TYSABRI should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Please see accompanying full Prescribing Information, including Boxed Warning.



Important Responsibilities

PRESCRIBERS—Among the important responsibilities of prescribers in the TOUCH Prescribing Program are the following:

- Acknowledge that TYSABRI should only be prescribed in accordance with the FDA label
- Educate the patient on the benefits and risks of treatment with TYSABRI by using the Patient Medication Guide
- Evaluate the patient 3 and 6 months after the first infusion, and every 6 months thereafter, and for 6 months after TYSABRI has been discontinued
- Determine every 6 months whether the patient should continue on treatment, and if so, reauthorize treatment
- Submit to Biogen Idec the TYSABRI Patient Status Report and Reauthorization Questionnaire 6 months after initiating treatment and every 6 months thereafter
- Report serious opportunistic infections and atypical infections with TYSABRI to Biogen Idec at 1 800 456 2255 and to the Food and Drug Administration's MedWatch program at 1 800 FDA 1088

PATIENTS—Among the important responsibilities of patients in the TOUCH Prescribing Program are the following:

- Bring to each infusion a list of all medicines and treatments they have taken during the last month
- Read the Patient Medication Guide before starting TYSABRI and before each TYSABRI infusion
- Promptly report any continuously worsening symptoms that persist over several days to their prescriber
- Inform all of their physicians that they are receiving TYSABRI
- Plan to see their prescriber 3 and 6 months after the first infusion, and at least as frequently as every 6 months thereafter

INFUSION SITES—Among the important responsibilities of infusion sites in the TOUCH Prescribing Program are the following:

- Confirm that the patient is currently authorized to receive TYSABRI
- Provide the patient with a copy of the TYSABRI Patient Medication Guide *prior to each infusion*
- Administer the Pre infusion Patient Checklist to every patient prior to each infusion and submit to Biogen Idec within 1 business day, regardless of whether the patient is infused or not

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