

Initial REMS Approval: 10/2011
Last modified/revised: 10/2016

BLA 125104

TYSABRI® (natalizumab) Intravenous Injection

Monoclonal Antibody

**Biogen, Inc
14 Cambridge Center
Cambridge, MA 02142**

(617) 679-2000

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

**TYSABRI Outreach: Unified Commitment to Health (TOUCH®) Prescribing
Program (MS & CD)**

I. GOALS:

The goals of the TYSABRI REMS are:

1. 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.
2. To warn against concurrent use with antineoplastic, immunosuppressant, or immunomodulating agents, and in patients who are immunocompromised.
3. To promote early diagnosis of PML and timely discontinuation of TYSABRI in the event of suspected PML.

II. REMS ELEMENTS:

A. Medication Guide

A Medication Guide (MG) for TYSABRI will be dispensed to each patient prior to each TYSABRI infusion in accordance with 21 CFR 208.24.

Please see the appended Medication Guide.

B. Elements to Assure Safe Use

1. Healthcare providers who prescribe TYSABRI are specially certified.

- A. Biogen will ensure that health care providers who prescribe TYSABRI are specially certified.
- B. To become certified, prescribers will be required to enroll in the TOUCH® Prescribing Program by completing the following requirements:
 - i. Review the TYSABRI REMS prescriber educational materials, including the full Prescribing Information.
 - ii. Complete and sign the Prescriber/Patient Enrollment Form and acknowledge the following:
 - a) I have read and understand the full Prescribing Information for TYSABRI
 - b) I understand that TYSABRI increases the risk of progressive multifocal leukoencephalopathy (PML), an opportunistic viral infection of the brain that usually leads to death or severe disability. When initiating and continuing treatment with

Initial REMS Approval: 10/2011

Last modified/revised: 10/2016

TYSABRI, I should consider whether the expected benefit of TYSABRI is sufficient to offset this risk

- c) I am aware that cases of PML have been reported in patients taking TYSABRI who were recently or concomitantly treated with immunomodulators or immunosuppressants, as well as in patients receiving TYSABRI monotherapy
- d) I understand that three risk factors identified thus far that increase the risk of PML in TYSABRI-treated patients are:

- Longer treatment duration, especially beyond 2 years
- Prior treatment with an immunosuppressant (e.g., mitoxantrone, azathioprine, methotrexate, cyclophosphamide, mycophenolate mofetil)
- The presence of anti-JCV antibodies.

These factors should be considered in the context of expected benefit when initiating and continuing treatment with TYSABRI.

- e) I understand that MRI findings may be apparent before clinical signs or symptoms. Periodic monitoring for radiographic signs consistent with PML should be considered to allow for an early diagnosis of PML. Lower PML-related mortality and morbidity have been reported following TYSABRI discontinuation in patients with PML who were initially asymptomatic compared to patients with PML who had characteristic clinical signs and symptoms at diagnosis.
- f) To my knowledge, this patient has no known contraindications to TYSABRI, including PML
- g) I have instructed this patient to promptly report to me any new or worsening symptoms that persist over several days, especially nervous system symptoms
- h) I understand that this patient should be seen and evaluated 3 months after the first infusion, 6 months after the first infusion, every 6 months thereafter for as long as this patient receives TYSABRI, and for at least 6 months after TYSABRI has been discontinued
- i) I will determine every 6 months whether this patient should continue on TYSABRI and, if so, authorize treatment for another 6 months
- j) I understand that I am required to submit an “Initial Discontinuation Questionnaire” when TYSABRI is discontinued and a “6-Month Discontinuation Questionnaire” following discontinuation of TYSABRI.

Initial REMS Approval: 10/2011

Last modified/revised: 10/2016

- k) I should report to Biogen, as soon as possible, cases of PML, hospitalizations due to opportunistic infection, or deaths
- l) I understand that data concerning this patient and me will be entered into the mandatory TOUCH Prescribing Program. Biogen requires my cooperation with periodic data collection. Failure to provide the requested information or otherwise comply with the requirements of the TOUCH Prescribing Program may result in discontinuation of TYSABRI treatment for this patient and termination of my authorization to prescribe TYSABRI
- m) I have received educational materials regarding the benefits and risks of TYSABRI treatment
- n) I have, or another healthcare provider under my direction has, educated this patient on the benefits and risks of treatment with TYSABRI, provided him or her with the Patient Medication Guide and Enrollment Form, instructed him or her to read these materials, and encouraged him or her to ask questions when considering TYSABRI

Acknowledgments specific to Multiple Sclerosis (MS)

- o) I understand that TYSABRI is indicated as monotherapy for relapsing forms of MS
- p) I understand that this patient has a relapsing form of MS based on clinical and radiological evidence
- q) I understand that TYSABRI increases the risk of progressive multifocal leukoencephalopathy (PML), an opportunistic viral infection of the brain that usually leads to death or severe disability. When initiating and continuing treatment with TYSABRI, I should consider whether the expected benefit of TYSABRI is sufficient to offset this risk
- r) I understand that TYSABRI is not ordinarily recommended for patients who are receiving chronic immunosuppressant or immunomodulatory therapy, or who are significantly immunocompromised from any other cause
- s) I understand that an MRI should be performed prior to initiating therapy with TYSABRI in MS patients

Acknowledgments specific to Crohn's Disease (CD)

- t) I understand that TYSABRI is indicated for adult patients with moderately to severely active 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

Initial REMS Approval: 10/2011

Last modified/revised: 10/2016

- u) I understand that patients receiving TYSABRI should not take concomitant immunosuppressants (e.g., 6-mercaptopurine, azathioprine, cyclosporine, or methotrexate) or inhibitors of TNF- α
- v) I understand that this patient has moderately to severely active CD with evidence of inflammation
- w) I have discussed other Crohn's disease treatments with this patient
- x) I understand that TYSABRI should be discontinued if a patient has not experienced a therapeutic benefit by 12 weeks of therapy
- y) I understand that patients receiving steroid therapy at the time of TYSABRI initiation must undergo a steroid tapering regimen once a therapeutic response is achieved. If the patient with Crohn's disease cannot be tapered off of steroids within six months of starting TYSABRI, TYSABRI should be discontinued

C. Biogen will:

- i. Ensure that prescriber enrollment can successfully be completed
- ii. Ensure that prescribers receive the TYSABRI prescribing information and the following materials that are part of the TYSABRI REMS and are appended:
 - TOUCH Prescribing Program Educational Slide Set
 - TOUCH Prescribing Program Enrollment Kits (specific to MS or CD)
 - TOUCH Prescribing Program Overview
 - Medication Guide
 - Prescriber/Patient Enrollment Form (MS or CD)
 - Pre-Infusion Patient Checklist (combined MS and CD)
 - Helpful Information for Evaluation of New Neurologic Symptoms in Patients Receiving TYSABRI (MS)
 - Understanding PML for Gastroenterologists (CD)
 - TOUCH On-Line (www.TOUCHPROGRAM.com)
 - Change Prescriber Authorization Form
 - 12 Week Questionnaire for Crohn's Disease
 - Patient Status Report and Reauthorization Questionnaire (specific to MS and CD)

Initial REMS Approval: 10/2011

Last modified/revised: 10/2016

- Initial Discontinuation Questionnaire (specific to MS or CD)
- 6-Month Discontinuation Questionnaire (specific to MS or CD)
- iii. Ensure that enrollment forms are complete before activating a prescriber's enrollment in the TOUCH Prescribing Program.
- iv. Ensure that prescribers are notified when they are successfully enrolled in the TOUCH Prescribing Program, and therefore, are certified to prescribe TYSABRI.

2. TYSABRI will be dispensed only by pharmacies and infusion sites that are specially certified.

- a. Biogen will ensure that certified pharmacies that dispense TYSABRI are specially certified.
- b. Pharmacies that dispense TYSABRI to infusion sites must enroll in the Tysabri TOUCH Prescribing Program by submitting a completed enrollment form and designating a person with appropriate authority to acknowledge the following:
 - i. The pharmacy has received training and educational materials on the TOUCH Prescribing Program
 - ii. I understand that certified pharmacies may dispense TYSABRI only to authorized infusion sites
 - iii. I understand that, per the requirements of the TOUCH Prescribing Program, this certified pharmacy's compliance may be reviewed by the Food and Drug Administration (FDA) and/or audited by Biogen and/or a third party designated by Biogen.
 - iv. I understand that noncompliance with the requirements of the TOUCH Prescribing Program may result in my pharmacy no longer being enrolled and termination of our participation in the program.
- c. Biogen will:
 - i. Ensure that pharmacies are notified when they are successfully enrolled in the TOUCH Prescribing Program, and therefore, are certified to dispense TYSABRI.
 - ii. Ensure the pharmacies that dispense TYSABRI to authorized infusion sites have been trained on the known risks, potential benefits, and appropriate use of TYSABRI using approved educational materials
- d. The following materials are part of the TYSABRI REMS and are appended:
 - TOUCH Prescribing Program Educational Slide Set

Initial REMS Approval: 10/2011

Last modified/revised: 10/2016

- TOUCH Prescribing Program Overview
 - Certified Pharmacy Enrollment Form
- e. Biogen will ensure that infusion sites where TYSABRI is dispensed and administered are specially certified.
- i. Infusion sites that dispense and administer TYSABRI must enroll in the TOUCH Prescribing Program by submitting a completed Infusion Site Enrollment Form and designating a person with appropriate authority to acknowledge the following:
- a) The infusion site has received training and educational materials on the TOUCH Prescribing Program
 - b) I understand that TYSABRI will be administered only to patients who are currently authorized in the TOUCH Prescribing Program. Patient authorization must be confirmed *prior to each infusion* by:
 - 1) For TOUCH On-Line infusion sites: Patient Authorization Status must be “Authorized” or
 - 2) For paper-based infusion sites: Receipt of current Notice of Patient Authorization and verification that no Notice of Patient Discontinuation is on file
 - c) I understand that each patient will receive a copy of the TYSABRI Patient Medication Guide *prior to each infusion*
 - d) I understand that a TYSABRI Pre-infusion Patient Checklist must be completed *prior to each infusion*. The Pre-infusion Patient Checklist must be submitted to Biogen within 1 business day of the patient visit, regardless of whether or not the patient received the infusion, by:
 - 1) For paper-based infusion sites: sending a copy of the completed Pre-infusion Patient Checklist to Biogen. A copy must also be placed in the patient’s medical record
 - 2) For TOUCH On-Line infusion sites: The infusion nurse can read, complete and submit the Pre-Infusion Patient Checklist directly in TOUCH On-Line
 - e) I understand that, per the requirements of the TOUCH Prescribing Program, this infusion site’s compliance with the REMS may be reviewed by FDA and/or audited by Biogen and/or a third party designated by Biogen.
 - f) I understand that noncompliance with the requirements of the TOUCH Prescribing Program will result in de-enrollment of the infusion site.
- f. Biogen will:

Initial REMS Approval: 10/2011

Last modified/revised: 10/2016

- i. Ensure that infusion sites are notified when they are successfully enrolled in the TYSABRI REMS Program, and therefore, are certified to dispense and administer TYSABRI.
 - ii. Ensure that infusion sites that dispense and administer TYSABRI have been trained on the known risks, potential benefits, and appropriate use of TYSABRI using approved educational materials.
- g. The following materials are a part of the TYSABRI REMS and are appended:
- TOUCH Prescribing Program Educational Slide Set
 - TOUCH Prescribing Program Overview
 - Infusion Site Enrollment Form
 - Pre-Infusion Patient Checklist
 - Medication Guide

3. TYSABRI will be dispensed to patients with evidence or other documentation of safe-use conditions.

- a. Biogen will ensure that certified prescribers enroll all patients into the TOUCH Prescribing Program by completing the Prescriber/Patient Enrollment Form for each new patient.
- b. A completed and signed Prescriber/Patient Enrollment Form must be submitted to Biogen before the patient may receive an infusion.

The Prescriber/Patient Enrollment Form requires the patient to acknowledge the following:

- i. I understand that TYSABRI increases my chance of getting a rare brain infection that usually leads to death or severe disability
 - a) This infection is called progressive multifocal leukoencephalopathy (PML). PML usually happens in people with weakened immune systems
 - b) There is no known treatment, prevention, or cure for PML
 - c) I should call my doctor right away if I get any new or worsening symptoms that last several days, especially nervous system symptoms, while I am taking TYSABRI, and for at least 6 months after I stop taking TYSABRI. Some of these symptoms include a new or sudden change in my thinking, eyesight, balance, or strength, but I should also report other new or worsening symptoms
 - d) My chance for getting PML increases if I:

Initial REMS Approval: 10/2011

Last modified/revised: 10/2016

- 1) Have received TYSABRI for a long time especially longer than 2 years
- 2) Have received certain medicines that can weaken my immune system before I start receiving TYSABRI
- 3) Have been exposed to John Cunningham Virus (JCV). JCV is a common virus that is harmless in most people but can cause PML in people who have weakened immune systems, such as people taking TYSABRI. Most people who are exposed to JCV do not know it or have any symptoms. This exposure usually happens in childhood. My doctor may do a blood test to check if I have been exposed to JCV before I start receiving TYSABRI or during my treatment

My risk of getting PML is greatest if I have all 3 risk factors listed above. There may be other risk factors for getting PML during TYSABRI treatment that we do not know about yet. My doctor should discuss the risks and benefits of TYSABRI treatment with me before I decide to receive TYSABRI.

ii. Acknowledgments specific to MS

I understand that TYSABRI is a medicine approved to treat patients with relapsing forms of multiple sclerosis (MS)

- a) TYSABRI increases the risk of PML. I understand that when starting and continuing treatment with TYSABRI, I should talk to my doctor about whether the expected benefit of TYSABRI is enough to outweigh this risk (see important information about PML below)
- b) I have talked to my doctor and understand the benefits and risks of TYSABRI treatment
- c) My chance for getting PML may be higher if I am also being treated with other medicines that can weaken my immune system, including other MS treatments. Even if I use TYSABRI alone to treat my MS, I can still get PML

iii. Acknowledgments specific to CD

I understand that TYSABRI is a medicine approved to treat patients with moderate to severe Crohn's Disease who have not been helped enough by, or cannot tolerate, usual Crohn's disease medicines and medicines called tumor necrosis factor (TNF) inhibitors

- a) I have talked to my doctor and understand the benefits and risks of TYSABRI treatment
- b) I understand that I should not take certain medicines that weaken the immune system while I am taking TYSABRI
- c) My chance for getting PML may be higher if I am also being treated with other medicines that can weaken my immune system, including other Crohn's disease

Initial REMS Approval: 10/2011

Last modified/revised: 10/2016

treatments. Even if I use TYSABRI alone to treat my Crohn's disease, I can still get PML.

- c. To receive TYSABRI all patients must be enrolled in a special program called the TOUCH Prescribing Program.
 - i. The TOUCH Prescribing Program is run by the company that makes TYSABRI. Under this program, the company is required to collect information about my health at regular time periods. I cannot receive TYSABRI if I do not agree to follow the requirements of the TOUCH Prescribing Program
 - ii. The company may use my information to meet the requirements of the TOUCH Prescribing Program, including helping me locate an authorized infusion site
 - iii. I must notify the TOUCH Prescribing Program if I switch physicians or infusion sites
 - iv. I have received, read, and understand the Patient Medication Guide
 - v. I will bring to each TYSABRI infusion a list of all medicines and treatments that I have taken during the last month

The following materials are part of the TYSABRI REMS and are appended:

- Prescriber/Patient Enrollment Forms (specific to MS or CD)
- Medication Guide

Biogen will make these materials available for the enrolled prescribers to provide to their patients.

C. Implementation System

The Implementation system for the TYSABRI REMS includes the following:

- a. Biogen must maintain a secure, validated database of all certified prescribers, certified pharmacies, certified infusion sites, and enrolled patients in the TOUCH Prescribing Program. The TOUCH Prescribing Program is an integrated, computerized, validated database that captures enrollment, patient tracking, and drug distribution data.
- b. Biogen will monitor the distribution of TYSABRI to ensure that the drug is only delivered to certified pharmacies and infused by certified infusion sites.
- c. Biogen will monitor the compliance of certified entities (i.e. pharmacies, infusion sites, and prescribers) as acknowledged in the signed entity specific enrollment form and, if appropriate, institute corrective actions, which could include retraining and de-enrollment
- d. Biogen will maintain TOUCH On-Line, which is an internet-based system that will allow enrolled TOUCH Prescribing Program participants the option of real-time access to view

Initial REMS Approval: 10/2011

Last modified/revised: 10/2016

and/or submit required or pertinent patient therapy information collected through the TOUCH Prescribing Program, such as information on the Pre-infusion Patient Checklist, the TYSABRI Patient Status Report and Reauthorization Questionnaire, and the TYSABRI Patient Discontinuation Questionnaire.

- e. Biogen will monitor and evaluate the implementation of the elements to assure safe use and take reasonable steps to work to improve implementation of these elements.

D. Timetable for Submission of Assessments of the REMS

Biogen will submit REMS Assessments annually from the date of the initial approval of the REMS (October 7, 2011). To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. Biogen will submit each assessment so that it will be received by the FDA on or before the due date.