HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TYSABRI safely and effectively. See full prescribing information for TYSABRI.

TYSABRI (natalizumab) injection for intravenous use
Initial U.S. Approval: 2004

WARNING: PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY
See full prescribing information for complete boxed 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 (5.1)
- Monitor patients, and withhold TYSABRI immediately at the first sign or symptom suggestive of PML (4, 5.1)
- TYSABRI is available only through a special restricted distribution program called the TOUCH™ Prescribing Program and must be administered only to patients enrolled in this program (5.1, 5.2)

----------RECENT MAJOR CHANGES ----------

Indications and Usage	
Crohn's Disease (1.2)	1/2008
Dosage and Administration	
Crohn's Disease (2.2)	1/2008
Warnings and Precautions	
Progressive Multifocal Leukoencephalopathy (5.1)	10/2008
Distribution Program for TYSABRI (5.2)	1/2008
Immunosuppression/Infections (5.4)	1/2008
Hepatotoxicity (5.5)	1/2008

----------INDICATIONS AND USAGE ----------

TYSABRI is an integrin receptor antagonist indicated for treatment of:

Multiple Sclerosis (MS) (1.1)

- 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. TYSABRI is generally recommended for patients who have had an inadequate response to, or are unable to tolerate, an alternate MS therapy.

Crohn's Disease (CD) (1.2)

- Inducing and maintaining clinical response and remission in adult patients with moderately to severely active Crohn's disease with evidence of inflammation who have had an inadequate response to, or are unable to tolerate, conventional CD therapies and inhibitors of TNF-α.

Important Limitations:

- In CD, TYSABRI should not be used in combination with immunosuppressants or inhibitors of TNF-α.

----------DOSAGE AND ADMINISTRATION ----------

- 300 mg infused intravenously over approximately one hour, every four weeks. Do not give as an intravenous push or bolus (2.1, 2.2).
- TYSABRI solution must be administered within 8 hours of preparation (2.3).
- Observe patients during the infusion and for one hour after the infusion is complete (2.4).
- In CD, discontinue in patients that have not experienced therapeutic benefit by 12 weeks of induction therapy, and in patients that cannot discontinue chronic concomitant steroids within six months of starting therapy (2.2).

----------DOSAGE FORMS AND STRENGTH ----------

- Solution [300 mg per 15 mL vial] for dilution prior to infusion (3).

----------CONTRAINDICATIONS ----------

- Patients who have or have had PML (4).
- Patients who have had a hypersensitivity reaction to TYSABRI (4).

----------WARNINGS AND PRECAUTIONS----------

- Progressive Multifocal Leukoencephalopathy (PML): Has occurred in patients who received TYSABRI. Patients who have significantly compromised immune system function should not ordinarily be treated with TYSABRI. Obtain an MRI scan in MS patients prior to initiating TYSABRI. Monitor MS and CD patients and withhold TYSABRI at the first sign or symptom suggestive of PML (5.1).
- Hypersensitivity reactions: Serious hypersensitivity reactions (e.g., anaphylaxis) have occurred. Permanently discontinue TYSABRI if such a reaction occurs (5.3).
- Immunosuppression/Infections: TYSABRI may increase the risk for certain infections. Monitor patients for development of infections due to increased risk with use of TYSABRI (5.4).
- Hepatotoxicity: Clinically significant liver injury has occurred. Discontinue TYSABRI in patients with jaundice or evidence of liver injury (5.5).

----------ADVERSE REACTIONS ----------

The most common adverse reactions (incidence ≥ 10%) in MS were headache, fatigue, arthralgia, urinary tract infection, lower respiratory tract infection, gastroenteritis, vaginitis, depression, pain in extremity, abdominal discomfort, diarrhea NOS, and rash; and in CD were headache, upper respiratory tract infections, nausea, and fatigue (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Biogen Idec or Elan at 1-800-456-2255 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------USE IN SPECIFIC POPULATIONS---------- ----------

- Pregnancy: Physicians are encouraged to enroll pregnant patients in the TYSABRI Pregnancy Exposure Registry by calling 1-800-456-2255 (8.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 10/2008

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the Full Prescribing Information are not listed.

TYSABRI® (natalizumab) Injection
FULL PRESCRIBING INFORMATION

WARNING: PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY

TYSABRI increases the risk of progressive multifocal leukoencephalopathy (PML), an opportunistic viral infection of the brain that usually leads to death or severe disability. 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 as monotherapy[see *Warnings and Precautions (5.1)*].

- **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 and Precautions (5.1, 5.2)*].**

- **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 (4), Warnings and Precautions (5.1)*].**

1 INDICATIONS AND USAGE

1.1 Multiple Sclerosis (MS)

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 progressive multifocal leukoencephalopathy (PML), an opportunistic viral infection of the brain that usually leads to death or severe disability, TYSABRI is generally recommended for patients who have had an inadequate response to, or are unable to tolerate, an alternate multiple sclerosis therapy [see *Boxed Warning, Warnings and Precautions (5.1)*].

Safety and efficacy in patients with chronic progressive multiple sclerosis have not been studied.

1.2 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 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 [see *Boxed Warning, Warnings and Precautions (5.1)*].

2 DOSAGE AND ADMINISTRATION

2.1 Multiple Sclerosis (MS)

Only prescribers registered in the MS TOUCH™ Prescribing Program may prescribe TYSABRI for multiple sclerosis [see *Boxed Warning, Warnings and Precautions (5.2)*]. The recommended dose of TYSABRI for multiple sclerosis is 300 mg intravenous infusion over one hour every four weeks.

2.2 Crohn's Disease (CD)

Only prescribers registered in the CD TOUCH™ Prescribing Program may prescribe TYSABRI for Crohn's disease [see *Boxed Warning, Warnings and Precautions (5.1)*].

The recommended dose of TYSABRI for Crohn's disease is 300 mg intravenous infusion over one hour every four weeks. TYSABRI should not be used with concomitant immunosuppressants (e.g., 6-mercaptopurine, azathioprine, cyclosporine, or methotrexate) or concomitant inhibitors of TNF-α. Aminosalicylates may be continued during treatment with TYSABRI.

If the patient with Crohn's disease has not experienced therapeutic benefit by 12 weeks of induction therapy, discontinue TYSABRI. For patients with Crohn's disease that start TYSABRI while on chronic oral corticosteroids, commence steroid tapering as soon as a therapeutic benefit of TYSABRI has occurred; if the patient with Crohn's disease cannot be tapered off of oral corticosteroids within six months of starting TYSABRI, discontinue TYSABRI. Other than the initial six-month taper, prescribers should consider discontinuing TYSABRI for patients who require additional steroid use that exceeds three months in a calendar year to control their Crohn's disease.

2.3 Dilution Instructions

(1) Use aseptic technique when preparing TYSABRI solution for intravenous infusion. Each vial is intended for single use only.
(2) TYSABRI is a colorless, clear to slightly opalescent concentrate. Inspect the TYSABRI vial for particulate material and discoloration prior to dilution and administration. If visible particulates are observed and/or the liquid in the vial is discolored, the vial must not be used.
(3) To prepare the solution, withdraw 15 mL of TYSABRI concentrate from the vial using a sterile needle and syringe. Inject the concentrate into 100 mL 0.9% Sodium Chloride Injection, USP. No other IV diluents may be used to prepare the TYSABRI solution.
(4) Gently invert the TYSABRI solution to mix completely. Do not shake. Inspect the solution visually for particulate material prior to administration.
(5) The final dosage solution has a concentration of 2.6 mg/mL.
(6) Following dilution, infuse TYSABRI solution immediately, or refrigerate solution at 2 to 8°C, and use within 8 hours. If stored at 2 to 8°C, allow the solution to warm to room temperature prior to infusion. DO NOT FREEZE.

2.4 Administration Instructions

- Infuse TYSABRI 300 mg in 100 mL 0.9% Sodium Chloride Injection, USP, over approximately one hour (infusion rate approximately 5 mg per minute). Do not

administer TYSABRI as an intravenous push or bolus injection. After the infusion is complete, flush with 0.9% Sodium Chloride Injection, USP.

- Observe patients during the infusion and for one hour after the infusion is complete. Promptly discontinue the infusion upon the first observation of any signs or symptoms consistent with a hypersensitivity-type reaction [see *Warnings and Precautions (5.3)*].
- Use of filtration devices during administration has not been evaluated. Other medications should not be injected into infusion set side ports or mixed with TYSABRI.

3 DOSAGE FORMS AND STRENGTHS

TYSABRI is a concentrated solution that must be diluted prior to intravenous infusion. TYSABRI injection is supplied as 300 mg natalizumab in 15 mL (20 mg/mL) in a sterile, single-use vial free of preservatives.

4 CONTRAINDICATIONS

- TYSABRI is contraindicated in patients who have or have had progressive multifocal leukoencephalopathy (PML) [see *Boxed Warning, Warnings and Precautions (5.1)*].
- TYSABRI should not be administered to a patient who has had a hypersensitivity reaction to TYSABRI. Observed reactions range from urticaria to anaphylaxis [see *Warnings and Precautions (5.3)*].

5 WARNINGS AND PRECAUTIONS

5.1 Progressive Multifocal Leukoencephalopathy (PML)

Progressive multifocal leukoencephalopathy, an opportunistic infection caused by the JC virus that typically only occurs in patients who are immunocompromised, developed in three patients who received TYSABRI in clinical trials [see *Boxed Warning*]. Two cases of PML were observed among 1869 patients with multiple sclerosis treated for a median of 120 weeks. The third case occurred among 1043 patients with Crohn's disease after the patient received eight doses. Both multiple sclerosis patients were receiving concomitant immunomodulatory therapy and the Crohn's disease patient had been treated in the past with immunosuppressive therapy. In the postmarketing setting, additional cases of PML have been reported in multiple sclerosis patients who were receiving no concomitant immunomodulatory therapy. 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. There are no known interventions that can reliably prevent PML or adequately treat PML if it occurs. It is not known whether early detection of PML and discontinuation of TYSABRI will mitigate the disease. There is limited experience beyond two years of treatment. The relationship between the risk of PML and the duration of treatment is unknown, but most cases of PML were in patients who received more than one year of treatment.

Ordinarily, patients receiving chronic immunosuppressant or immunomodulatory therapy or who have systemic medical conditions resulting in significantly compromised immune system function should not be treated with TYSABRI. The incidence of PML appears to be lower in patients receiving TYSABRI as monotherapy; however, the number of cases is too few and the number of patients treated too small to reliably conclude that the true risk of PML is lower in patients

treated with TYSABRI alone than in patients who are receiving other drugs that decrease immune function or who are otherwise immunocompromised.

Because of the risk of PML, TYSABRI is available only under a special restricted distribution program, the TOUCH™ Prescribing Program.

In multiple sclerosis 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.

In Crohn's disease patients, a baseline brain MRI may also be helpful to distinguish pre-existent lesions from newly developed lesions, but brain lesions at baseline that could cause diagnostic difficulty while on TYSABRI therapy are uncommon.

Healthcare professionals should monitor patients on TYSABRI for any new sign or symptom suggestive of PML. Typical symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes. The progression of deficits usually leads to death or severe disability over weeks or months. Withhold TYSABRI dosing 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. There are no known interventions that can adequately treat PML if it occurs. Three sessions of plasma exchange over 5 to 8 days were shown to accelerate TYSABRI clearance in a study of 12 patients, 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. There is no evidence that plasma exchange has any benefit in the treatment of opportunistic infections such as PML.

5.2 Distribution Program for TYSABRI

TYSABRI is available only under 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. 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). TYSABRI must be administered only to patients who are enrolled in and meet all the conditions of the MS or CD TOUCH™ Prescribing Program. Contact the TOUCH™ Prescribing Program at 1-800-456-2255 [see *Boxed Warning*].

To enroll in the TOUCH™ Prescribing Program, prescribers and patients are required to understand the risks of treatment with TYSABRI, including PML and other opportunistic infections. Prescribers are required to understand the information in the Prescribing Information and to be able to:

- Educate patients on the benefits and risks of treatment with TYSABRI, ensure that the patient receives the Medication Guide, instruct them to read it, and encourage them to ask questions when considering TYSABRI. Patients may be educated by the enrolled prescriber or a healthcare provider under that prescriber's direction.
- Review the TOUCH™ Prescriber/Patient Enrollment form for TYSABRI with the patient and answer all questions.
- As part of the initial prescription process for TYSABRI, obtain the patient's signature and initials on the TOUCH™ program enrollment form, sign it, place the original signed

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